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Faculdade de Farmácia

Departamento de Química Farmacêutica e Terapêutica

Development of New Methodologies for C-H Insertion

Luís Filipe Rodrigues Gomes

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Development of New Methodologies for C-H Insertion

Luís Filipe Rodrigues Gomes

Tese orientada pelo Prof.º Doutor Carlos A. M. Afonso, especialmente elaborada para a obtenção do grau de doutor no ramo de Farmácia, especialidade de Química Farmacêutica e Terapêutica

Abstract

Antibiotics are a fundamental tool for modern medicine to treat bacterial infections. One of the first antibiotics to be discovered was penicillin which is a natural occurring β-lactam isolated form *Penicillium* fungi. β-lactam-derived antibiotics own a broad antibacterial spectrum, clinical efficiency and an excellent safety profile. This made them one of the antibiotics still more prescribed. The chemical manipulation of this core allowed more potent variants which increased the demand for such processes. Among these the C-H insertion reaction with C-C bond formation offers new possibilities of retrosynthetic disconnections on β-lactam synthesis by dirhodium (II)-catalyzed α-diazoacetamides decomposition. This catalyst has two axial positions and on one of them a N-heterocyclic carbene (NHC) was previously complexed but the authors claimed that this NHC was instable and was removed during the catalytic cycle. We used other monocoordinated NHCs ligands which showed to be stable on this position on α-diazoacetamides decomposition. Longer reaction times were observed as well as a preference for β-lactam over γ-lactam formation and a decarbonylated product derived from the Wolff rearrangement was also observed.

Since diazo compounds are potentially explosive and toxic reagents their use is very restricted to large scale applications, despite being a common laboratorial reagent. Therefore the demand for a stable surrogate is highly demanded. Here, iodonium ylides were used for the C-H insertion with C-C bond formation for the synthesis of β-lactams and up to good yields were obtained under very smooth conditions. The method here developed is diazo- and transition metal-free. Besides, the substrate activation and subsequent C-H insertion reaction occurs in a single synthetic step, instead of the two usually required for the diazo moiety transfer and its decomposition. Mechanistic experiments allowed to propose that the C-H insertion also occurs *via* a carbene intermediate.

Keywords: Beta-lactam; C-H insertion; Carbene; Dirhodium; NHC; Iodonium Ylide; Diazo.

Resumo

Os antibióticos são uma ferramenta fundamental na medicina moderna no tratamento de infeções bacterianas. Um dos primeiros antibióticos a ser descoberto foi a penicilina que é uma β-lactama de origem natural isolada do fungo *Penicillium.* Os antibióticos derivados de β-lactamas possuem um amplo espectro antibacteriano, eficiência clinica e segurança comprovada. Estas características fizeram delas uma das classes de antibióticos mais prescritas. A manipulação química deste núcleo permitiu variantes mais potentes o que por sua vez aumentou a procura por estes processos. Entre estes a reação de inserção C-H com formação de ligações C-C oferece novas possibilidades na desconexão retrossintética na síntese de β-lactamas por decomposição de α-diazoacetmidas catalisada por diródio (II). Este catalisador possui duas posições axiais e numa delas foi previamente complexado um carbeno N-heterocíclico (NHC) mas os autores afirmaram que este NHC era instável e era removido durante o ciclo catalítico. Nós usámos outros ligandos de NHC monocoordenados que demostraram serem estáveis nesta posição durante a decomposição de α-diazoacetmidas. Foram observados tempos reacionais mais longos bem como a preferência pela formação de β-lactamas em vez de γ-lactamas e um produto de descabonilação derivado do rearranjo de Wolff também foi observado.

Dado que os compostos diazo são reagentes potencialmente explosivos e tóxicos o seu uso está muito restrito em aplicações em grande escala, apesar de serem vulgares no laboratório. Deste modo existe uma grande procura por um substituto dos diazos. Aqui os iletos de iodónio foram usados na inserção C-H com formação de ligações C-C na síntese de β-lactamas e foram obtidos bons rendimentos em condições muito suaves. O método aqui desenvolvido não utiliza metais nem compostos diazo. Além da ativação do substrato e subsequente inserção C-H, a reação ocorre apenas num passo sintético, em alternativa dos dois vulgarmente necessários para a transferência do diazo e a sua decomposição. Experiências mecanísticas permitiram concluir que a inserção C-H também ocorre tendo um carbeno por intermediário.

Palavras-Chave: β-lactama; Inserção C-H; Carbeno; Diródio; NHC; Ileto de Iodónio; Diazo.

Acknowledgements

The work here presented reports the beginning of my journey through the field of Organic Chemistry. I feel truly lucky to have shared so many good moments with so many bright people who passed me not only their enthusiasm, but also their knowledge. They also deserve my recognition for their help, advice and support.

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Abbreviations

Adam	Adamantyl
bs	Broad singlet
cap	Caprolactamate
cat.	Catalytic
COD	1,5-Cyclooctadiene
d	Duplet
DBU	1,8-Diazabicycloundec-7-ene
DFT	Density functional theory
DIB	(Diacetoxyiodo)benzene
DME	1,1-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EDG	Electrondonating group
EI	Electronic impact
eq.	Equivalent
ESI	Electrospray ionization
EWG	Electronwithrawing group
FAB	Fast atom bombardment
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IB	Iodosobenzene
IR	Infrared spectroscopy
J	Nuclear magnetic resonance coupling constant
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Multiplet
m.p.	Melting point
m/z	Mass-to-charge ratio

m-CPBA	3-Chloroperbenzoic acid
MS	Mass spectrometry
MW	Microwave heating
n.d.	Not detected
NBS	N-Bromosuccinimide
n-Bu	*n*-Butyl
NCS	N-Chlorosuccinimide
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
oct	octanoate
p	Pentet
p-ABSA	*para*-Acetamidobenzenesulfonyl azide
PCC	Pyridinium chlorochromate
pfb	Perfluorobutyrate
Piv	Pivaloyl
ppm	Parts per million
PTC	Phase transfer catalyst
q	Quartet
Refl.	Reflux
R_f	Retardation factor
R_t	Retention time
s	Singlet
sp	Septet
t	Triplet
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
tfa	Trifluoroacetate

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Troc	2,2,2-Trichlorethoxycarbonyl
Ts	Tosyl
WI	Wiberg index

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1. DISSERTATION OVERVIEW

The production of molecules with high biological activity is of paramount importance for the modern society. The pharmaceutical industry assumed a leading role on all drug development stages, since the drug discovery process to its large scale production and commercialization. In this context, antibiotics have contributed to treat routine or life-threatening bacterial infections and are now established drugs. Since the discovery of sulfonamides and penicillins, they have saved millions of people from certain death and ease the pain of much more patients. Penicillins are a class of β-lactam antibiotics which is still in use and the initial natural isolated molecules have evolved into more sophisticated semisynthetic variants. Now virtually every major pharmaceutical company has its research line on antibiotics development, to face the multi-drug resistant bacterias. Therefore new methods for the β-lactam ring preparation both in small and large scales are desired.

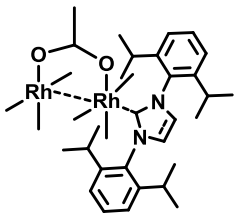
On pharmaceutical companies, medicinal and synthetic chemists work together to develop new methods of β-lactam ring synthesis suitable for large scale production. The metal-catalyzed reactions play a decisive role on process efficiency for industrial applications though metal-free processes are also welcome. The dirhodium(II)-catalyzed C-H insertion with C-C bond formation from α-diazoacetamides is a very appealing method for the β-lactam ring construction despite the diazo reagents associated risks. The dirhodium(II) catalysts family has a bimetallic core and two axial positions where the diazo substrate can coordinate, among other features, it is believed that the other axial position remains free or solvated during the reaction. In order to evaluate the axial position influence on the C-H insertion reaction pathway, N-heterocyclic carbenes monocoordinated onto a dirhodium(II) catalyst were studied on α-diazoacetamides cyclization and a different reactional profile emerged. A chiral water-soluble dirhodium(II) complex was also studied.

The β-lactam ring synthesis via decomposition of α-diazoacetamides possesses many risks when the reaction is conducted on large scale because of the diazo moiety explosive behavior; besides diazo compounds are toxic and carcinogenic. They are usually synthesized from azides, which are also potentially explosive and toxic. Such hazardous can’t be tolerated on industrial scale and therefore this methodology is removed from the pharmaceutical company’s reactions portfolio, except few isolated

cases. Some already developed methodologies don't offer a true solution for this problem. Here it was intended to circumvent the diazo moiety drawback for the β-lactam ring synthesis. A diazo- and transition metal-free methodology was developed which also shorts the synthetic reactional steps by one, on β-lactam ring synthesis. The mechanism was also studied.

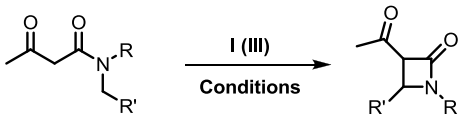
In summary the research presented in this thesis is divided into two main subjects:

Chapter 2



DIRHODIUM (II)-CATALYZED α-DIAZOACETAMIDES DECOMPOSITION

Chapter 3



DIAZO-FREE C-H INSERTION WITH C-C BOND FORMATION

Scheme 1: Dissertation overview.

Each chapter is framed by a state-of-the-art introduction where important developments on the field are exposed. It is followed by the results and discussion part where mechanistic experiments were also carried and then the conclusions.

Finally the experimental part of both chapters is included in the final where all the procedures are described, with spectral data and experimental procedures.

2. DIRHODIUM (II)-CATALYZED α-DIAZOACETAMIDES DECOMPOSITION

Abstract:

A previously reported dirhodium (II) complex with an axially monocoordinated NHC was not stable in carbene-mediated reactions, namely C-H insertion. The evidences gathered here show that other dirhodium(II)-NHCs complexes are stable for C-H insertions. The reactions often require longer times and the selectivity is different, where a Wolff-type rearrangement is responsible for a new product formation, mechanistically supported by experiments and DFT calculations.

A chiral water soluble Rh(II) catalyst did not afford promising results for cyclopropanation, ArOH insertion and ROH / [2,3] sigmatropic rearrangement for model substrates when compared with reported efficient catalytic systems.

Published articles *in peer* reviewed journals for this chapter:

- L. F. R. Gomes, A. F. Trindade, N. R. Candeias, P. M. P. Gois, C. A. M. Afonso*; *Tetrahedron Lett.* **2008**, *49*, 7372.
- L. F. R. Gomes, A. F. Trindade, N. R. Candeias, L. F. Veiros, P. M. P. Gois, C. A. M. Afonso*; *Synthesis-Stuttgart* **2009**, 3519.
- N. R. Candeias*, C. Carias, L. F. R. Gomes, V. André, M. T. Duarte, P. M. P. Gois, C. A. M. Afonso*; *Adv. Synth. Catal.* **2012**, *354*, 2921.

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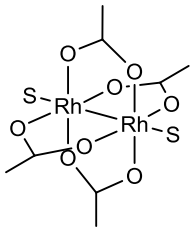
2.1. Introduction

2.1.1. Dirhodium (II) Complexes and C-H Insertion

The first dirhodium (II) complex was synthesized in the old Soviet Union in 1960 but described as a complex of Rh(I). Only later with its X-ray diffraction pattern it was proved to be a complex of dirhodium (II)[1]. Since then dirhodium (II) complexes evolved into a family which has applications as catalysts. This family of complexes contains a bimetallic structure with a single bond between the Rh centers, four equatorial bridging ligands which enhances its resistance and two axial positions, usually labile where the solvent or the substrate can coordinate[2] (Scheme 2). The dirhodium tetraacetate is commercially available and became one of the most simple catalysts of this family. It is commonly prepared by refluxing $RhCl_3$ with acetic acid and sodium acetate in ethanol[3]. The resulting green crystals after purification can be used as catalysts or to synthesize more complex catalysts[4].



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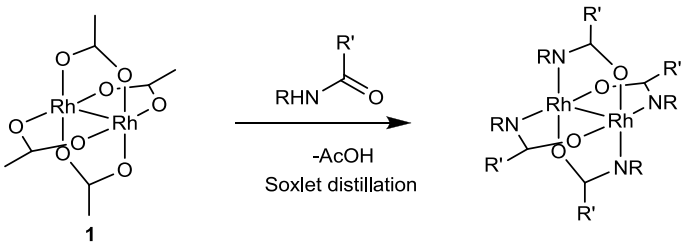
Scheme 2: The dirhodium tetraacetate structure with solvents on axial positions.

The equatorial ligands can be replaced by more sophisticated ones, often chiral, by refluxing the complex with the appropriate ligand in clorobenzene; a soxlet apparatus with potassium carbonate as acetic acid scavenger is usually employed to remove this ligand. Dirhodium (II) carboxamidates[5] are usually obtained by this method and these catalysts have an important role on C-H insertion[4a, 6] (Scheme 3).

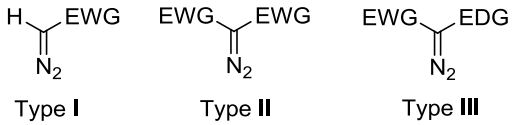


Scheme 3: General synthesis of dirhodium (II) tetracarboxamidates.

Dirhodium (II) complexes have biological activity as enzymes inhibitor[7] and carcinostatic agent[8]. They also can inhibit the DNA synthesis with low impact on RNA and protein synthesis[9].

Nowadays diazo compounds[10] are a common source of carbenes due to the easy dinitrogen release[11]. This reaction can be induced by several metals such as Cu[12], Pd[13] and Ru[14] but for C-H insertion dirhodium (II)[15] is the best suited catalysts. It affords very reactive complexed carbenoids[4a, 11, 16] which can undergo several transformations as olefin cyclopropanation or alkyne cyclopropenation; ylide transfer when reacting with X-H bonds (X= O, N, S) or the most characteristic reaction of this catalyst, the C-H insertion on an inactivated C-H bond to afford a new C-C bond. When chiral catalysts are employed the asymmetric induction can be very pronounced and quaternary stereocenters can also be formed[17].

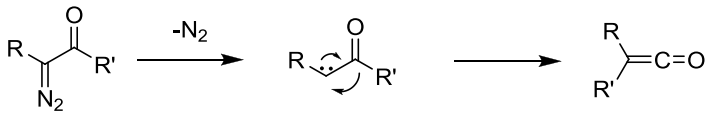
Diazo compound substrates can be divided into 3 groups accordingly to its substituents[4a] (Scheme 4): with just one electronwithdrawing (EWG) group, making them very reactive (I); two EWG (II) or one EWG and one electrondonating group (EDG) (III), making them more stable. Dirhodium (II) catalysts families display better enantio-induction accordingly their structure and substrate structure on a matched combination. Dirhodium (II) carboxamidates (Scheme 3) are better suited for type **I** substituents while dirhodium (II) carboxylates for type **II** and **III**.



Scheme 4: The diazo families for dirhodium (II) catalysis.

Diazo decomposition can also be performed thermally[18] and photochemically[19] providing free carbenes but these reactions are regarded with low synthetic utility. Free carbenes trend to be very reactive but when complexed their reactivity is smooth and

can engage on selective reactions, diminishing side reactions like the Wolff rearrangement[20] which can be completely suppressed (Scheme 5). Electronic and stereochemical factors on both catalyst and substrate can modify the sensitive reaction pathway.

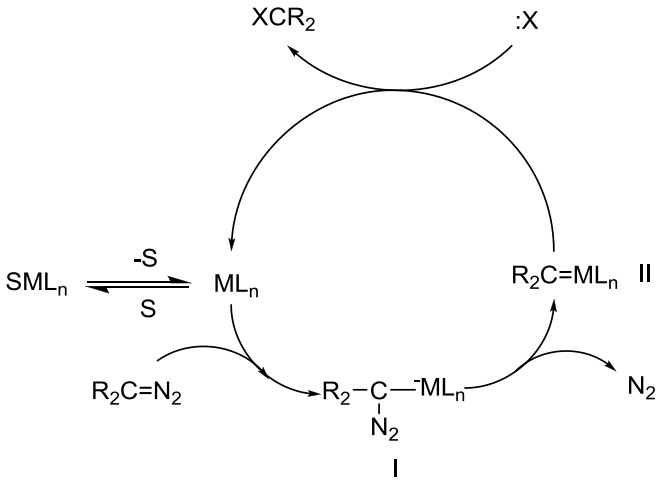


Scheme 5: The Wolff rearrangement.

The C-H insertion reaction has been object of deep research and several reviews are available[4a, 11, 15-16, 21].

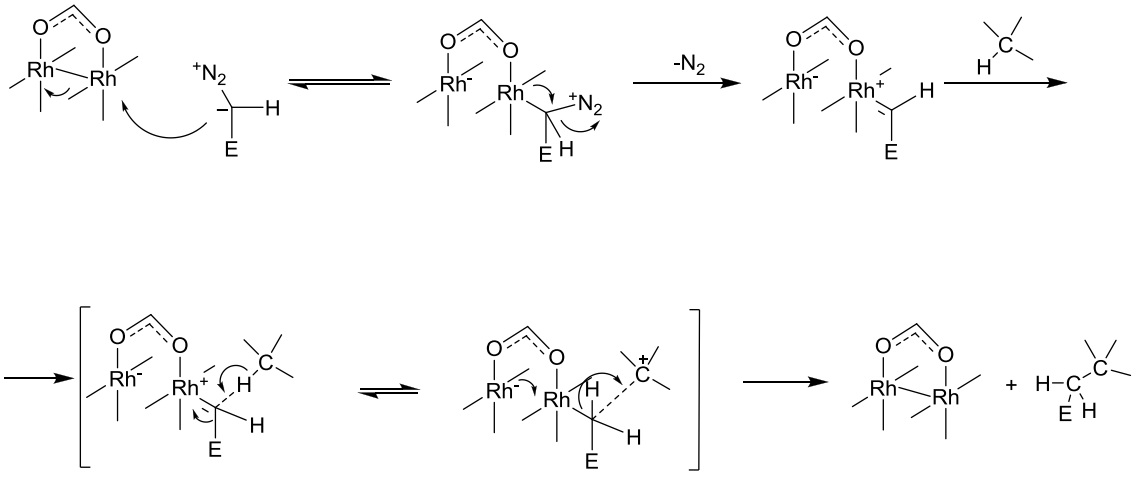
2.1.2. The C-H Insertion Mechanism with Dirhodium (II) Catalysts

The mechanism for the dirhodium (II) catalyzed diazo decomposition with C-H insertion / C-C bond formation was firstly proposed by Doyle[21d, 22] (Scheme 6). After the solvent decomplexation of an axial position the diazo's carbon attacks the electrophilic Rh center (intermediate I). The dinitrogen liberation occurs with metal carbenoid formation (intermediate II) which is transferred to an electronic rich C-H bond and the catalyst is regenerated.



Scheme 6: The catalytic cycle of diazo decomposition with C-H insertion.

Later, based on theoretical calculations Nakamura *et al.*[23] proposed a more accurate transition state where the nucleophilic attack of the diazo compound breaks the Rh-Rh bond (Scheme 7). Then the π-backdonation forces the nitrogen liberation, being this the limiting step. The C-H activation / C-C bond formation proceeds with in a single step through a tree-center hydride like transition state with a small activation energy. The second Rh assists the C-H insertion acting as a mobile ligand that enhances the carbenoid electrophilicity and assists the rhodium-carbon bond cleavage while reestablishing the Rh-Rh bond. The electronically more rich C-H bond reacts preferentially which is in agreement with the Nakamura's mechanism since is this one that generates the most stable carbocation. Therefore tertiary carbons are more reactive than secondary and these ones more than primary.

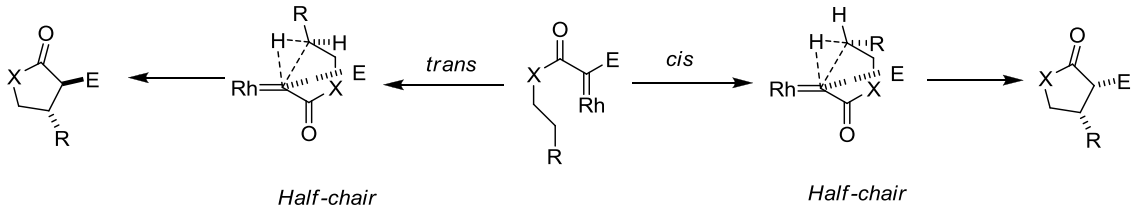


Scheme 7: The C-H insertion mechanism proposed by Nakamura *et al.*

Besides Nakamura's *et al.* computational studies[23] there are other evidences which link the rate limiting step to the dinitrogen extrusion such as kinetic isotope effects[24] and other reaction kinetic studies[25].

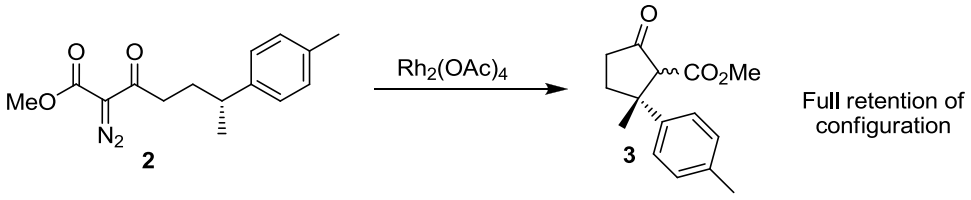
The intramolecular C-H insertion diastereoselectivity[26] was also studied by the same group using computational calculations[27], where an *n*-membered ring formation proceeds via n+1 membered cycle transition state involving the transferred H atom (Scheme 8). The stereoselectivities are controlled by the conformation of the n+1 membered ring which also depends of the substrate's substitution pattern. Therefore the most stable conformation has the bulky substituents on the equatorial position, minimizing the 1,3- diaxial repulsion. The steric environment created by the ligands has

a determining role as well. There is a general preference for five membered ring formations, since its transition state has a six-membered ring.



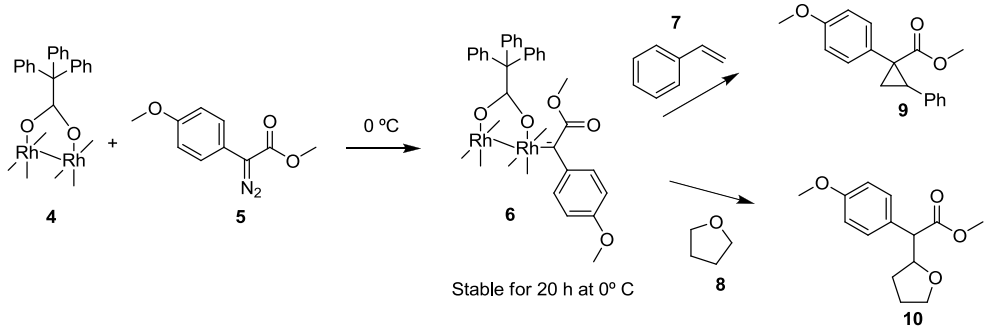
Scheme 8: The transitions state leading to *cis/trans* diastereoselectivities.

Taber *et al.* proved that the dirhodium (II)-catalyzed C-H insertion with C-C bond formation proceeds with full retention of absolute configuration and is therefore suitable for construction of quaternary stereocentes[28] (Scheme 9).



Scheme 9: The dirhodium (II)-catalyzed C-H insertion on chiral centers.

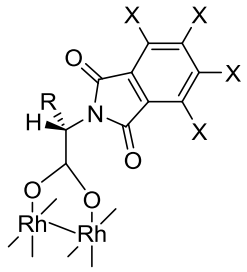
Dirhodium (II) carbenoids are very reactive and only recently was obtained a stable enough one to be characterized[29] (Scheme 10). It was synthesized with electrondonating groups both on catalyst and substrate and it was only stable at 0 ºC for 20 h. The ^{13}C NMR displayed a signal at 240 ppm corresponding to the carbenoid carbon. The activity was evaluated towards styrene cyclopropanation and C-H insertion on THF. On both cases similar reactivity was found when compared to the catalytic activity of catalyst **4**.



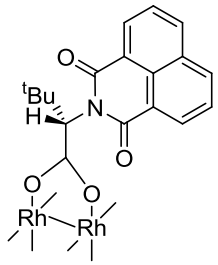
Scheme 10: Synthesis and reactivity of the first characterized dirhodium (II) carbenoid complex.

2.1.3. Dirhodium (II) Catalysts

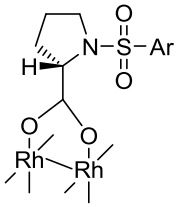
The equatorial ligands on the dirhodium tetraacetate complex can be easily replaced by chiral ones leading to asymmetric intramolecular or intermolecular C-H insertions. Several dirhodium (II) catalysts are available[4a, 15]. They are catalytically extremely active and regularly employed in 1 mol % loading or even less. The most used catalysts with carboxylate ligands are displayed on Scheme 11. These catalysts often take advantage of the chiral pool provided by naturally occurring α-aminoacids.



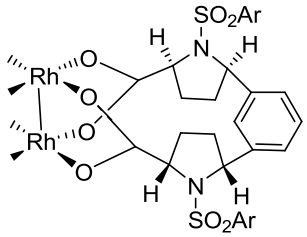
11 R= ^{t}Bu, X=H: Rh_2(*S*-PTTL)$_4$
12 R= Bz, X=H: Rh_2(*S*-PTPA)$_4$
13 R= ^{t}Bu, X=Cl: Rh_2(*S*-TCPTTL)$_4$
14 R= ^{t}Bu, X=Br: Rh_2(*S*-TBPTTL)$_4$
15 R= Adam, X=H: Rh_2(*S*-PTAD)$_4$



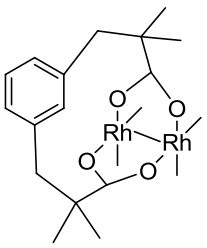
16 Rh_2(*S*-NTTL)$_4$



17 Ar= p-($C_{12}H_{25}$)C_6H_4, Rh_2(*S*-DOSP)$_4$
18 Ar=p-^{t}BuC_6H_4, Rh_2(*S*-TBSP)$_4$



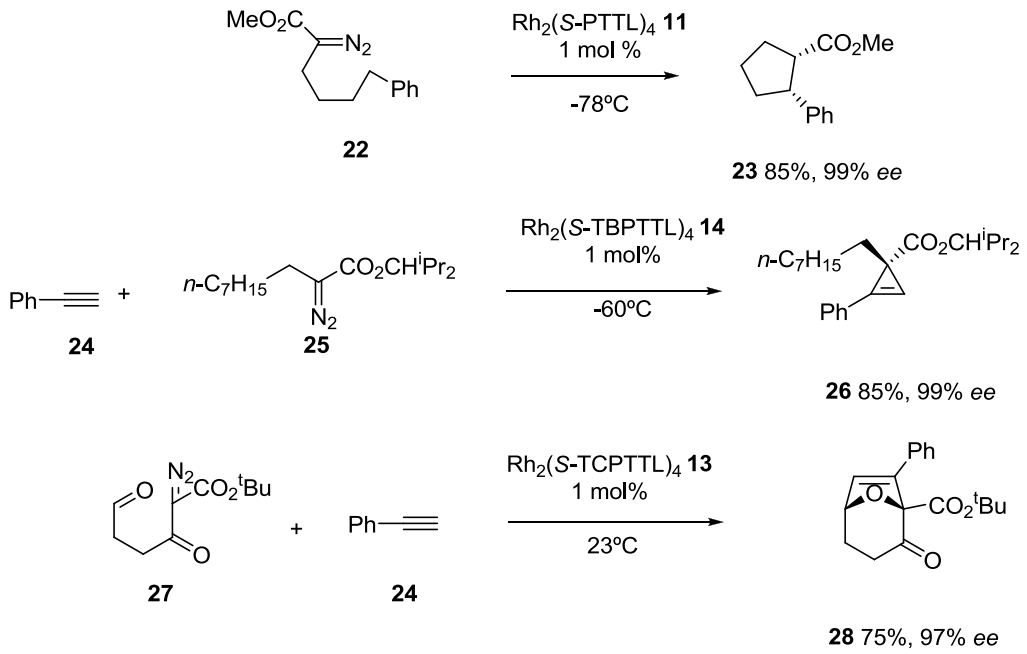
19 Ar= p-($C_{12}H_{25}$)C_6H_4, Rh_2(*S*-biDOSP)$_2$
20 Ar=2,4,6-^{i}PrC_6H_2, Rh_2(*S*-TBSP)$_2$



21 Rh_2(esp)$_2$

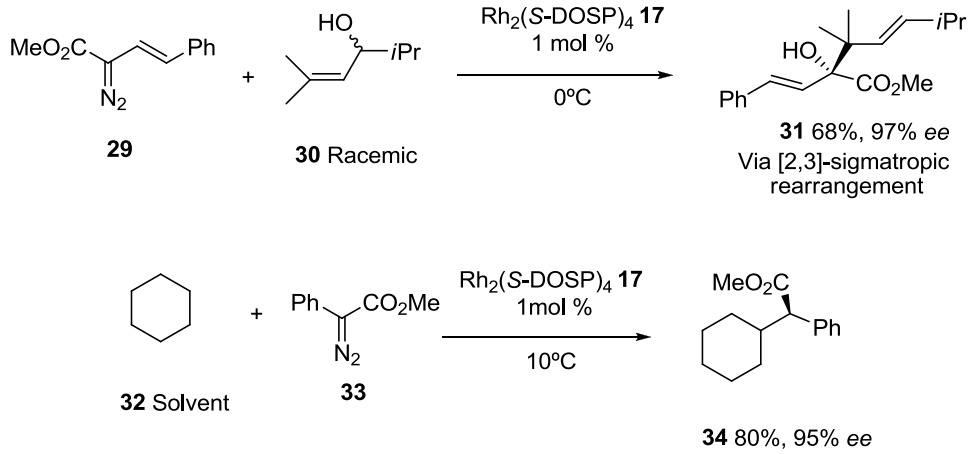
Scheme 11: Representative examples of dirhodium (II) tetracarboxylate catalysts.

Catalysts **11**-**14** are based on phthalimide protection of α-aminoacids and were introduced by Hashimoto's group namely **11** and **12** which display very good yields and *ee*'s on intramolecular C-H insertions[4a], and the halogenated ones **13**, **14** on cyclopropenation[30] and ylide chemistry[31] (Scheme 12). They provide better results for type II diazo compounds (Scheme 4).



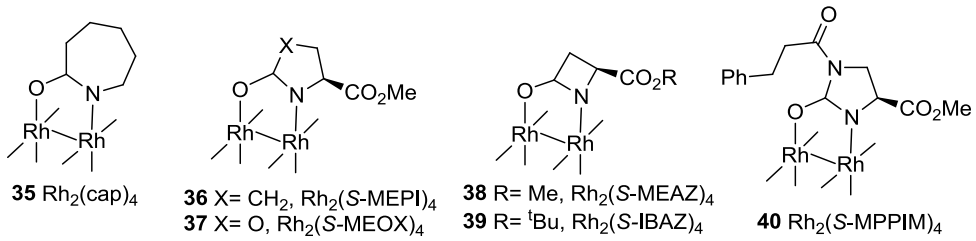
Scheme 12: Examples of reactions catalyzed by Hashimoto's catalysts.

The catalysts **17**-**20** based on proline were introduced by the Davies group. They are best suited for type III diazo compounds decomposition, in intramolecular[32] or even intermolecular reactions[33] (Scheme 13).



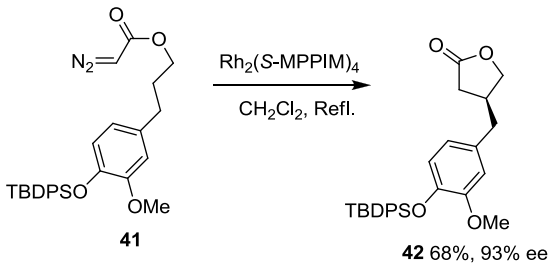
Scheme 13: Examples of reactions catalyzed by Davies's catalysts.

On Scheme 14 are presented some representative examples of the dirhodium (II) carboxamidate catalysts[15]. These often have an ester connected to the quiral center which is not only responsible for the chiral induction but also for the metal carbenoid 2*p* vacant orbital stabilization.



Scheme 14: Representative examples of dirhodium (II) tetracarboxamidate catalysts.

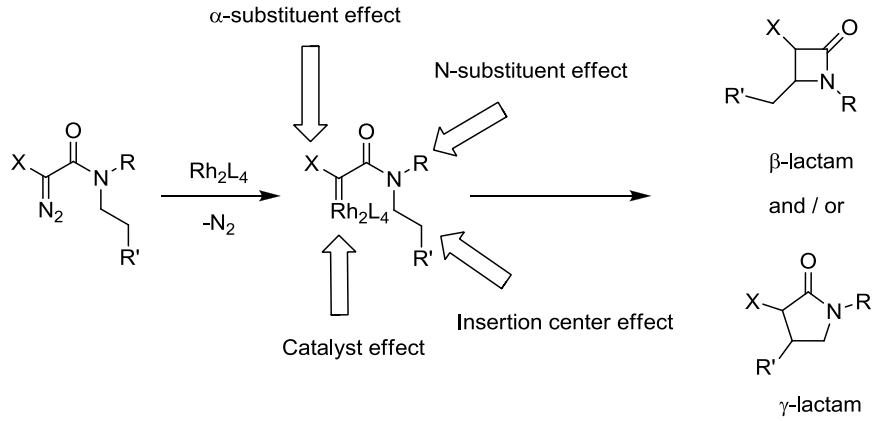
Dirhodium (II) carboxamidates are best suited for decomposition of diazo compounds[34] containing one EWG, type I (Scheme 15).



Scheme 15: Rh (II) carboxamidate-catalyzed C-H insertion.

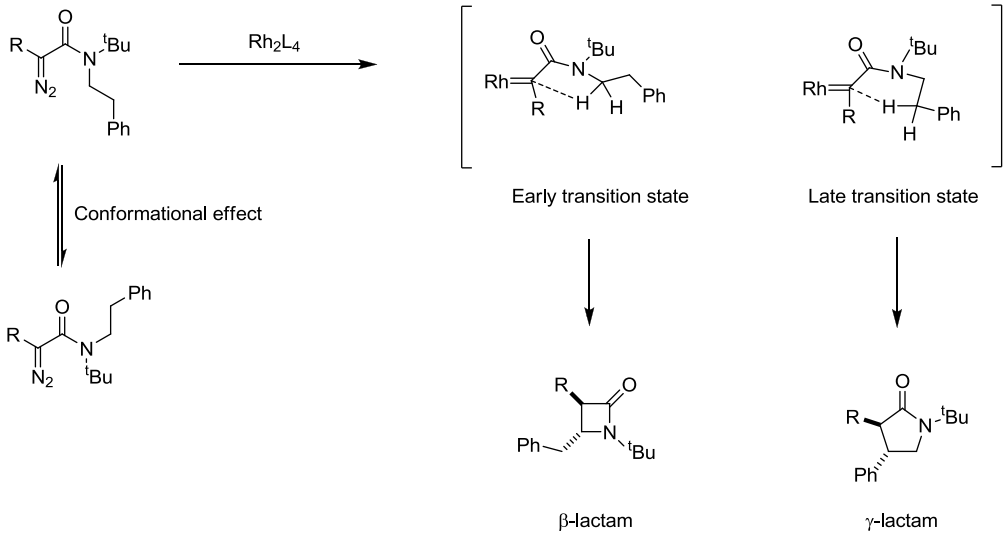
2.1.4. The C-H Insertion in α-Diazoacetamides

α-diazo acetamides are especially relevant substrates for the intramolecular C-H insertion[35] since can lead to β-lactam formation which are molecules of biological activity[36]. There are several factors which have influence the C-H insertion outcome (Scheme 16): 1) the catalyst effect, through the ligand substitution, and 2) the effects of the substrate namely the α-substituent, which controls the carbenoid electrophilicity; the substituent near the insertion center, which can activate or deactivate the nearby C-H position and the effect of the N-substituent which can modify the reaction selectivity.



Scheme 16: several effects on α-diazoacetamide cyclization**.**

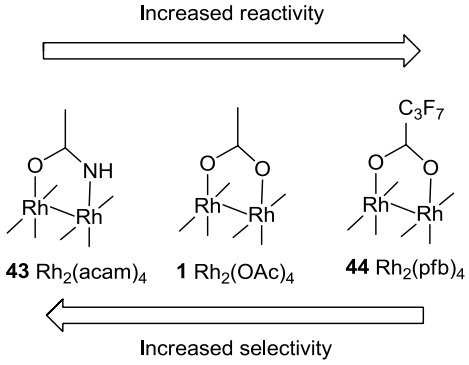
The combination of these effects produces different ratios of β- and γ-lactams (Scheme 17). While the β-lactam is obtained *via* an early transition state, the γ-lactam is obtained with a more stable carbenoid and *via* a late transition state[37] (6-membered ring).



Scheme 17: Transition states which give rise to β- and γ-lactams.

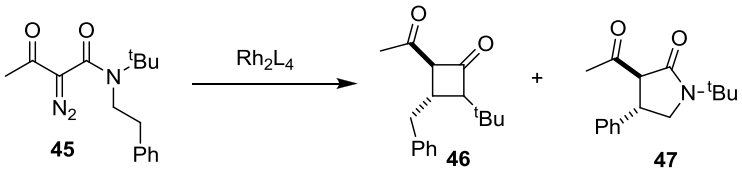
2.1.5. The Catalyst Effect

In order to occur the C-H insertion, the metal carbenoid requires an appropriate electrophilicity since too much attractor ligands make the carbenoid very reactive and consequently less selective. On the opposite side too much electrondonating ligands make the catalyst more selective, but the metal carbenoid formation requires more reactive substrates[35] (Scheme 18).



Scheme 18: Variation of catalysts reactivity and selectivity with ligands.

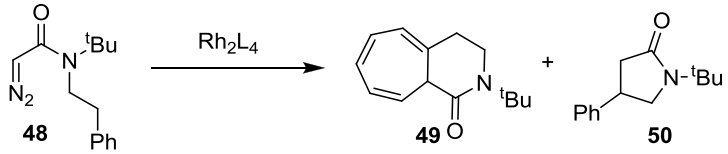
The ligand choice can influence the reaction regioselectivity (Scheme 19). Despite the γ-lactam **47** transition state has a 6-membered ring, the highly reactive catalyst $Rh_2(pfb)_4$ inverts this trend. On the opposite side, the carboxamidate ligand $Rh_2(acam)_4$ is the most selective[38].



Catalyst	Yield (%)	46	47
$Rh_2(pfb)_4$	85	56	44
$Rh_2(OAc)_4$	94	49	51
$Rh_2(acam)_4$	90	30	70

Scheme 19: Catalyst ligands influence on reaction regioselectivity.

Too much reactive substrates can provide significative amounts of **49,** the carbenoid aromatic addition product followed by cyclopropane ring opening, competing with the C-H insertion one **50**. By catalyst selection both products can be obtained selectively[39] (Scheme 20).

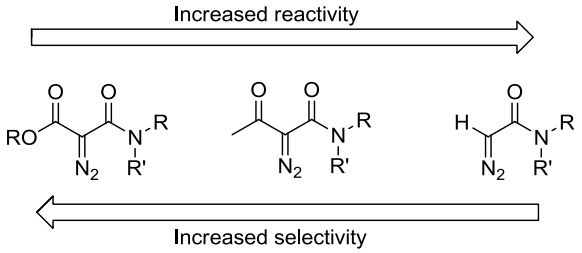


Catalyst	Yield (%)	49	50
$Rh_2(pfb)_4$	80	95	5
$Rh_2(OAc)_4$	85	68	32
$Rh_2(acam)_4$	80	23	77
$Rh_2(cap)_4$	82	3	97

Scheme 20: Catalyst ligands influence on C-H insertion *vs* aromatic substitution.

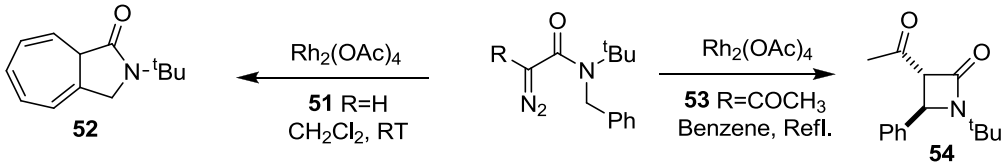
2.1.6. The α-Substituent Effect

The α-substituent plays an important role on the reaction first step: the metal carbenoid formation. As less the α-substituents electronattraction is, less is the tendency for the metal carbenoid formation, but once formed the reaction proceeds more selectively[35] (Scheme 21). Nonetheless electronattractor α-substituents are required for the diazo moiety stabilization.



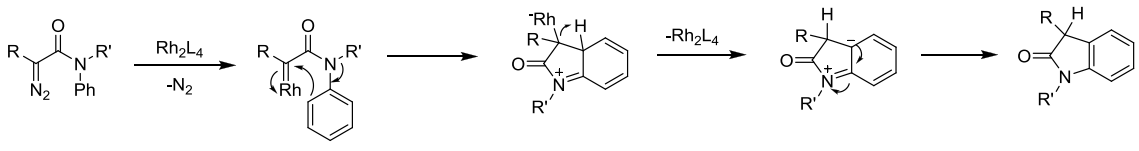
Scheme 21: Variation of selectivity and reactivity with α-substituent.

A dramatic effect is obtained on the cyclizations of **51** and **53** catalyzed by $Rh_2(OAc)_4$[40]. With the replacement of R=H by R=$COCH_3$ the C-H insertion product **54** is obtained instead of **52**.



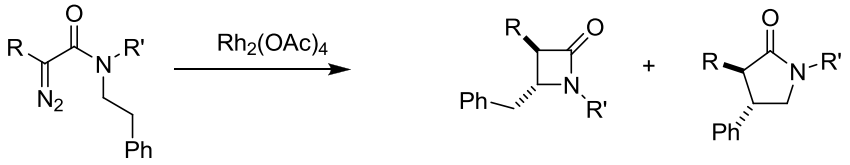
Scheme 22: The dramatic effect of the α-substituent.

A product of aromatic substitution can be obtained by another mechanism, which not the C-H insertion. It is believed that the reaction occurs *via* the aromatic ring nucleophilic attack to the metal carbenoid, followed by proton migration, catalyst dissociation and rearomatization (Scheme 23).



Scheme 23: The proposed mechanism for aromatic substitution product.

Another example of the α-substituent importance is presented on Scheme 24. Depending only on this substituent a mixture of β- and γ- lactam is obtained or exclusively the γ-lactam in excellent yields[35].

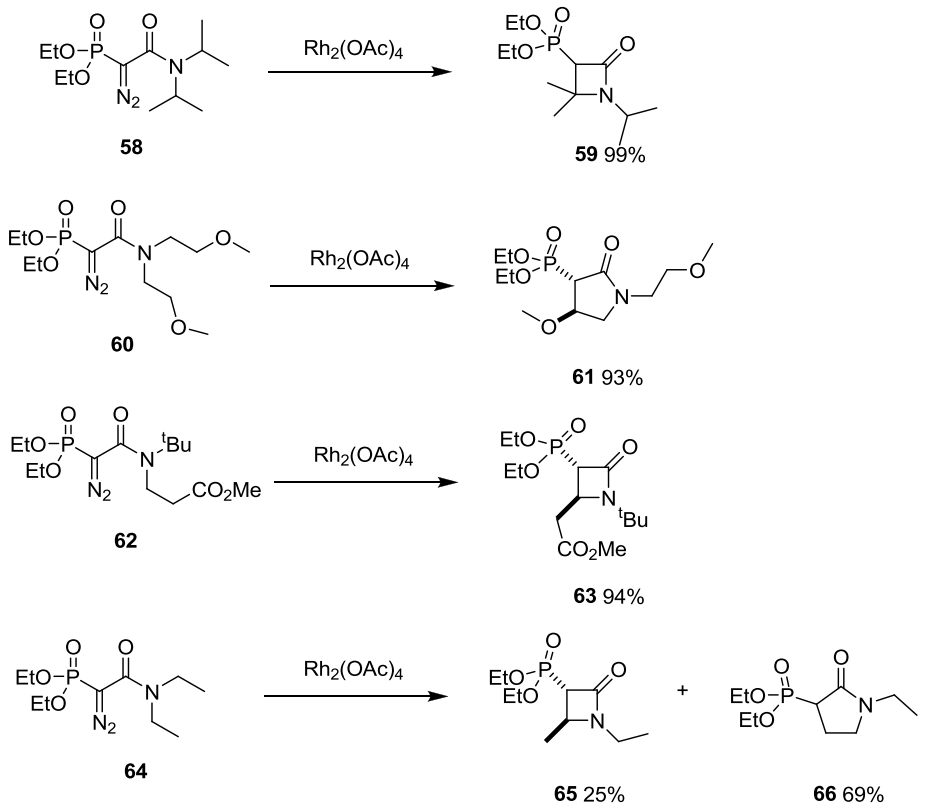


Substrate	R	R'	Yield (%)	β-lactam	γ-lactam
45	$COCH_3$	^tBu	94	49	51
55	CO_2CH_3	PMP	76	1	99
56	$PhSO_2$	^tBu	95	-	95
57	$PO(OEt)_2$	^tBu	95	-	95

Scheme 24: Selectivity variation with the α-substituent.

2.1.7. The Insertion Center Effect

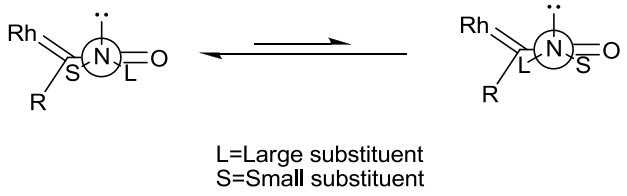
Despite the preference for γ-lactam formation due to its 6-membered ring transition state, the electronic effects may modify the reaction regioselectivity. Electrondonating groups near the insertion center facilitate here the C-H insertion, while electronwithdrawing groups penalize it[35] (Scheme 25). The C-H insertion on compound **58** only affords the β-lactam **59** due to the nearby methyl- and N-activations. With compound **60** the β-lactam is not obtained despite the nearby N. Instead only γ-lactam **61** is produced since the favorable transition state and the activating O nearby. On the other hand the deactivating ester group near the C-H insertion center can have a profound effect and with compound **62** in which only β-lactam **63** is obtained. A mixture of β- / γ-lactams is obtained when no strong influence is available as in case of compound **64**.



Scheme 25: The effect of nearby activating/ deactivating groups for the C-H insertion.

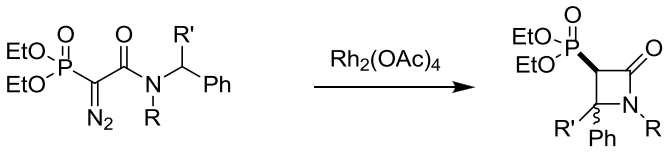
2.1.8. The N-Substituent Effect

The reaction regioselectivity can be modified by the conformational effects. When there is a marked volume difference between the N-substituents this effect is considerable. On the transition state the N non-bonding electrons overlap the carbonyl π system fixing the most stable conformation where the bulkiest group is placed *syn* to the carbonyl while the smaller group adopts a position near the metal carbenoid, which facilitates the C-H insertion[38] (Scheme 26). When this conformational effect is absent the selectivity can be lost.



Scheme 26: The conformation caused by bulky substituents.

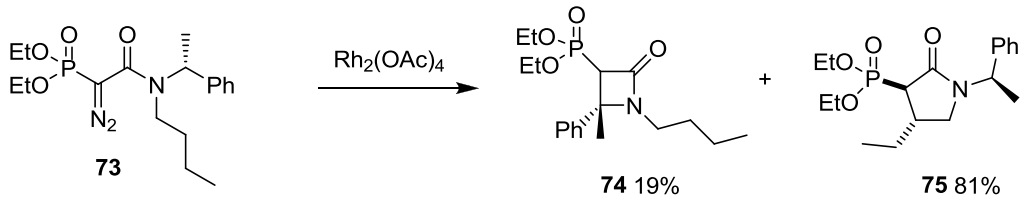
The bulky *tert*-butyl group can modify the reaction diastereoselectivity. The absence of this group on **67** cyclization produces more *trans*-**68**, but the *tert*-butyl introduction increases the repulsion between this group and the phenyl becoming the *cis*-isomer a better alternative[41] (Scheme 27).



Substrate	R	R'	Product	Reaction mixture		Yield
				cis	*trans*	(%)
67	CH_2Ph	H	**68**	5	95	81
69	^tBu	CH_3	**70**	60	40	75
71	^tBu	H	**72**	88	12	89

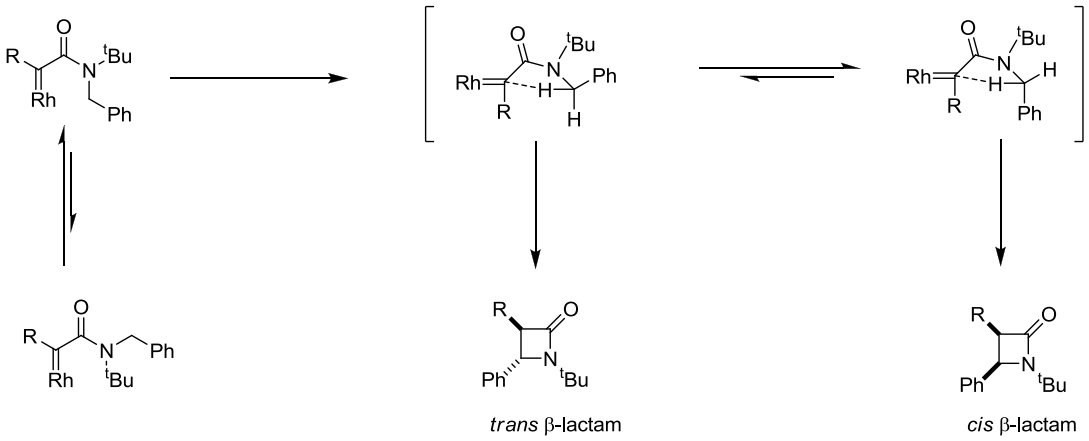
Scheme 27: Selectivity variation with the size of the N-substituents.

On the following example the benzylic position is the most activated one and the C-H insertion should occur on it (Scheme 28). Nonetheless the methyl group increases the size of this substituent and the formation of γ-lactam **75** is preferential[41].



Scheme 28: The effect of the N-substituent.

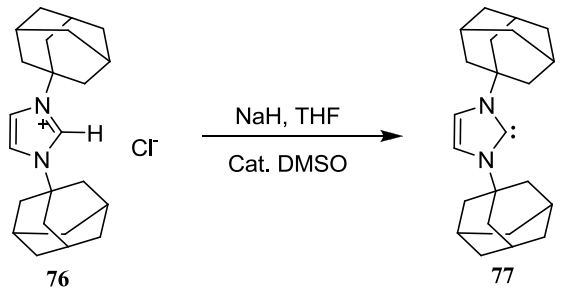
With the model presented in Scheme 26 applied to the diastereoselective preference on β-lactams formation, the transition state where the bulky *tert*-butyl is on equatorial position and the benzyl is on axial position leads to the *cis*-β-lactam, where the *trans*-β-lactam is disfavored[42] (Scheme 29).



Scheme 29: The conformational effect which induce the diastereoselectivity on β-lactams.

2.1.9. The N-Heterocyclic Carbenes

In 1991 Arduengo III *et al*. published the synthesis and characterization of the first stable crystalline carbene[43] (1,3-di-1-adamantylimidazol-2-ylidene, **77**). It was synthesized from **76** with NaH in THF and a catalytic amount of DMSO. **77** was isolated as colorless crystals and it's stable enough to be melted and the second melting has the same melting point and ^{1}H NMR spectrum than the initial sample. This high degree of stabilization is provided by steric and electronic effects[44] (Scheme 30). The steric constrains are provided by the bulky adamantyl groups and the electronic effects are caused by the N *p* non bonding electrons which stabilize the carbene's *p*-vacant orbital.

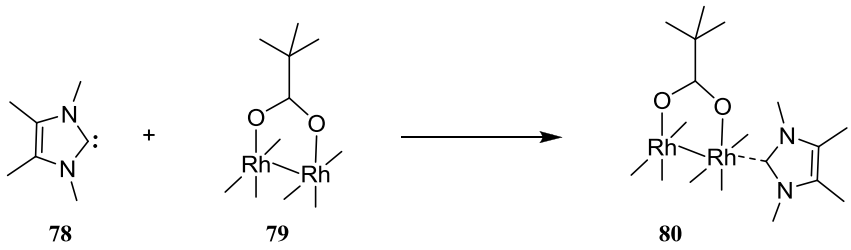


Scheme 30: Synthesis of the first stable crystalline carbene.

After this discovery the Arduengo's III laboratory published the synthesis of several stable carbenes. Once only theorized, now they have found widespread applications as metal ligands[45] and organocatalysts[46] also. On the C-H insertion / C-C bond formation reaction carbenoids play a central role as intermediates.

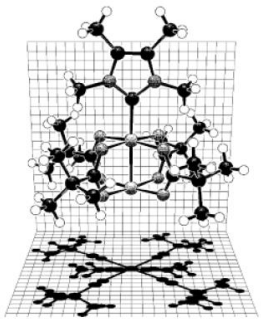
2.1.10. NHC's as Axial Dirhodium (II) Ligands

In 2001 Snyder, Arduengo III *et al.* published the first synthesis of a dirhodium (II) complex with a NHC on a axial position[47] (Scheme 31).



Scheme 31: The first dirhodium (II) complex with a NHC on axial position.

This complex **80** was isolated as whine red crystals and with the X-ray diffraction the conformation presented on Scheme 32 was obtained. The NHC ligand adopts a conformation where the N-C-Rh plan has an angle of 45º with the *trans*-O-Rh-O, reducing the steric hindrance.



Scheme 32: Model from X-ray diffraction of complex **80**.

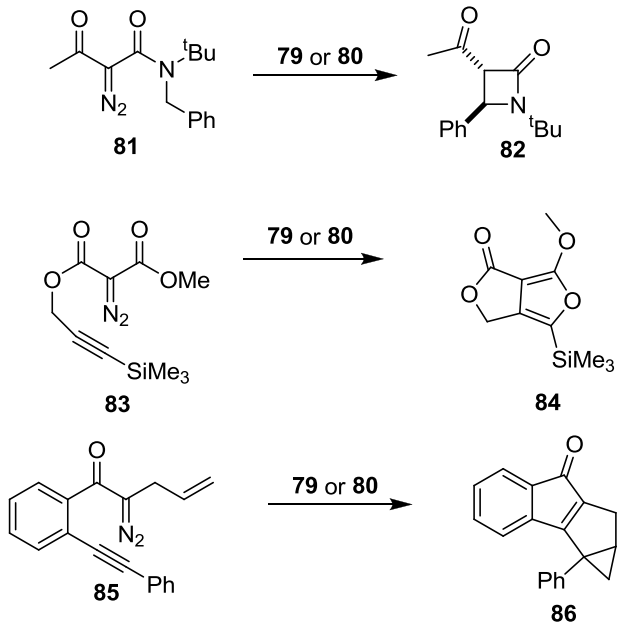
Another important feature of this complex is the Rh-Rh bond distance: an extension of 0.05 Å was obtained with comparison with the complexes $Rh_2(RCOO)_4$, R=H and R= C_3H_7 average. On Table 1 are displayed some distances and angles obtained with complex **80** by X-ray crystallography:

Distances (Å)		**Angles (º)**	
Rh-C	**Rh-Rh**	**N-C-N**	**N-C-Rh-O**
2.057	2.424	102.0	0.5-2.8

Table 1: Some relevant distances and angles on complex **80**.

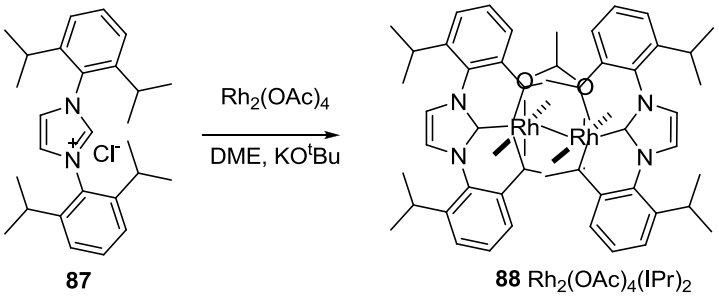
While on regular Rh=CHH carbenoid bond a half part of the electrons come from the carbenoid σ donation to the Rh center and the other half from the π backdonation from the Rh a carbenoid's *p* orbital, in **80** the π repulsion caused by the free N electrons opposes the Rh π backdonation and weakens the Rh-C bond. Therefore, this bond has a simpler bond character. It is only observed the complexation on a single axial position, the other remains free due to the broad σ donation from the NHC and the consequent *trans* effect, therefore the other NHC on the other axial position is labile. The DFT calculations reveal that both Rh are on +2 oxidation state and not one on +1 and the other on +3.

Catalysts **79** and **80** were tested to verify reactivity changes induced by the axial ligand **78**. Three experiments were conducted: one on intramolecular C-H insertion and two with intramolecular alkynes cyclization with 1 mol % of both catalysts (Scheme 33). The obtained products and yields were identical with both complexes. The authors justify the same reactivity with the decomplexation of the NHC **78** due to the weak bond and the reaction is catalyzed by the same dirhodium (II) complex **79**.



Scheme 33: Reactions to test catalyst **80**.

Our laboratory has synthesized other dirhodium (II) complexes with other NHCs on the axial position[48]. The carbene salt **87** is added to $Rh_2(OAc)_4$ and KO^tBu in DME.

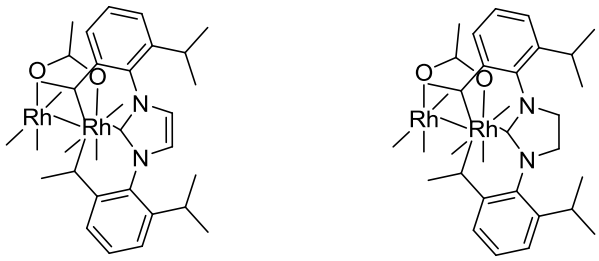


Scheme 34: Synthesis of $Rh_2(OAc)_4(IPr)_2$ complex.

In this case the complex containing two NHCs ligands on axial positions was obtained due to the weaker *trans* effect caused by the ligand. The isopropyl groups fit in between the acetate bridges and the carbene ring adopts an eclipsed conformation being aligned with the O-Rh-O axis, against the 45º on complex **80**. This stereochemical protection may help to stabilize the complex. Another similar complex may be obtained with a saturated imidazole backbone.

The complex with one NHC coordinated can be obtained by eluting the dimer **88** in a silica preparative thin layer chromatographic plate, where an NHC is loose and the pure complexes are obtained. The orange dimmer acquires the monomeric characteristic whine color during the chromatography. Both complexes with a NHC axially coordinated can be obtained, one with an unsaturated backbone **88** (NHC: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and a saturated **89** (NHC: 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene) (Scheme 35 and Scheme 36).

Scheme 35: X-ray structures of complexes **88** (left) and **89** (right).



88 $Rh_2(OAc)_4(IPr)$ **89** $Rh_2(OAc)_4(SIPr)$

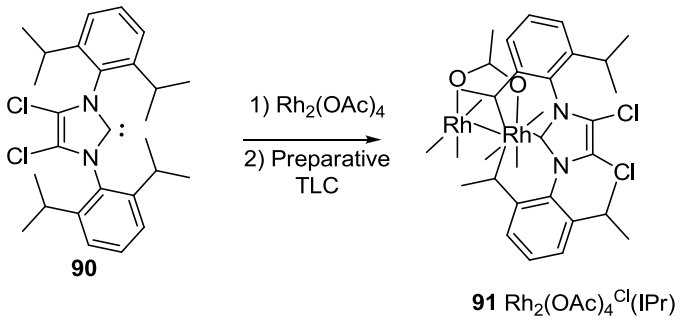
Scheme 36: The complexes of $Rh_2(OAc)_4$ with one axial NHC, **88** and **89**.

The mono NHC coordination causes a charge asymmetry on the rhodium at. DFT calculations on the unsaturated NHC complex **88** show a charge of 0.89 on the rhodium bonded to the NHC and 0.74 on the other one. The $Rh_2(OAc)_4$ **1** complex has a charge of 0.74 on both Rh centers. Some relevant distances obtained for both complexes **88** and **89** are displayed on Table 2:

	Distance (Å)			
	Monomer		Dimmer	
	Rh-C	**Rh-Rh**	**Rh-C**	**Rh-Rh**
89	2.114	2.426	2.228	2.473
88	2.126	2.417	2.244	2.463

Table 2: Selected bond distances for $Rh_2(OAc)_4$-NHC complexes obtained with X-Ray crystallography.

The complex with an unsaturated and chlorinated imidazole ring is obtainable[49] from the respective free carbene. The dimmer is also formed but by silica preparative thin layer chromatographic plate elution the monomer **91** is collected (Scheme 37).

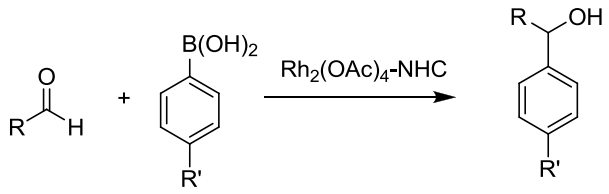


90 **91** $Rh_2(OAc)_4^{Cl}(IPr)$

Scheme 37: Complex of $Rh_2(OAc)_4$ with one axial NHC, **91**.

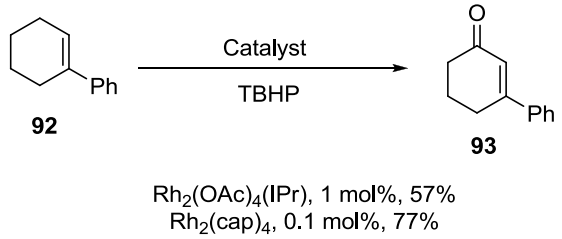
Catalysts $Rh_2(OAc)_4$(IPr) **88** and $Rh_2(OAc)_4$(SIPr) **89** were already used on arylation of aldehydes with arylboronic acids and were obtained isolated yields up to

99%[48a] (R=C_6H_5, R'=Me; Scheme 38). This Rh catalysis was only knew with Rh(I) complexes[50].



Scheme 38: Aldehyde arylation with $Rh_2(OAc)_4$-NHC complexes.

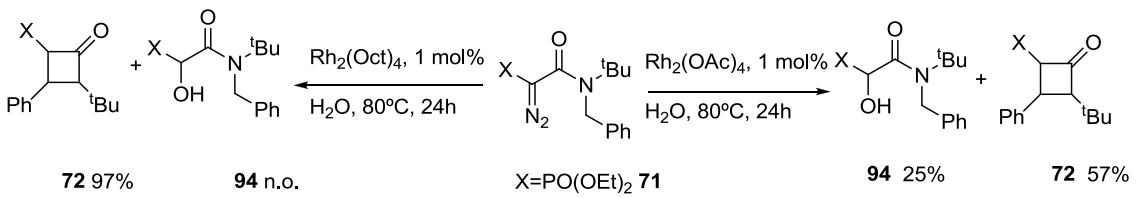
On an independent work Jang *et al.*[51] also synthesized the complex $Rh_2(OAc)_4$(IPr) **88**, by mixing the respective NHC carbene with $Rh_2(OAc)_4$ and used it on allylic oxidations. With $Rh_2(OAc)_4$ **1** the product **93** was obtained in only 9 % yield while with $Rh_2(OAc)_4$(IPr) **88** gave 57% yield. The dirhodium (II) catalyst better suited for this transformation is the $Rh_2(cap)_4$[52] (Scheme 39).



Scheme 39: Dirhodium (II) complexes usen on allylic oxidation.

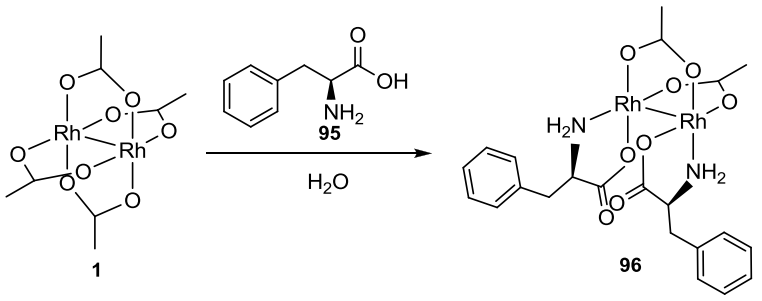
2.1.11. The Catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$

The C-H insertion reaction in water was firstly described by this laboratory[53]. It was found that hydrophobic effects promoted by the catalyst and by the substrate could avoid the water insertion over the C-H insertion pathway[54] (Scheme 40).



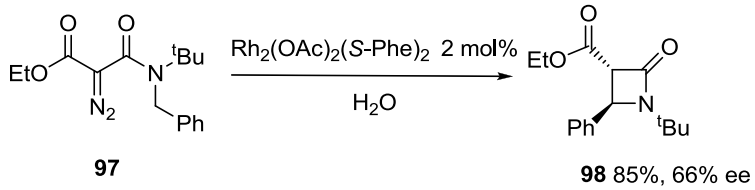
Scheme 40: H_2O insertion *vs* C-H insertion on catalyst-dependent reaction pathway; n.o.= not observed.

This prompted the laboratory to develop a water compatible asymmetric catalyst with α-aminoacids since water is an environmentally friendly solvent. After several α-aminoacids screening, *L*-phenylalanine was best suited and catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** was isolated (Scheme 41). Its uncommon structure was confirmed by single crystal X-ray diffraction[55].



Scheme 41: Structure of catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$.

Catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** can catalyze the reaction of substrate **97** in water in 85% yiled and 66% *ee*, the β-lactam formation (Scheme 42). This result confirms the utility of catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ for asymmetric C-H insertion in water. Furthermore the catalyst was reused for 7 runs maintaining good results.



Scheme 42: Decomposition of substrate **97** with catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$.

2.2. Results and Discussion

2.2.1. Decomposition of α-Diazoacetamides with $Rh_2(OAc)_4$-NHC Catalysts

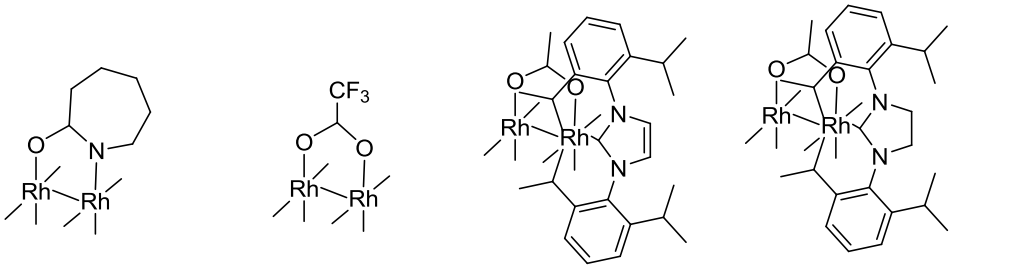
We aim to evaluate if the catalysts $Rh_2(OAc)_4$(IPr) **88**, $Rh_2(OAc)_4$(SIPr) **89** and $Rh_2(OAc)_4^{Cl}$(IPr) **91** are stable on C-H insertion conditions and if there is any reactivity variation caused by the mono coordinated NHC ligand compared to $Rh_2(OAc)_4$.

In 1991 Arduengo III *et al.* published the synthesis of the first stable carbene. Later Snyder and Arduengo III *et al.*[47] synthesized the first dirhodium (II) complex with an axially monocoordinated NHC. Complex **80** was then tested for intramolecular C-H insertion reaction and for alkynes intramolecular cyclizations with diazo compounds. They obtained identical results with this complex **80** and $Rh_2(piv)_4$ **79**. According to the authors complex **80** decomposes on the reactional medium and the reaction is only catalyzed by $Rh_2(OAc)_4$. Our laboratory also synthesized other dirhodium (II)-NHC complexes, $Rh_2(OAc)_4$(IPr) **88**, $Rh_2(OAc)_4$(SIPr) **89** and $Rh_2(OAc)_4^{Cl}$(IPr) **91** among others. These complexes have four isopropyl groups which provide steric hindrance to the NHC-Rh bond increasing its stability. Therefore these complexes can be stable to intramolecular C-H insertions and induce a reactivity variation since this reaction is strongly influenced by electronic effects.

The synthesis of catalyst $Rh_2(OAc)_4$(SIPr) was performed as reported and obtained in 80% yield. Initially to verify its stability it was heated under reflux of 1,2-dichloroethane for 24 h and the ^{1}H NMR spectrum didn't revealed decomposition. The catalytic performance in C-H insertion reactions was evaluated with α-diazoacetamides due to the several factors which influence their cyclization.

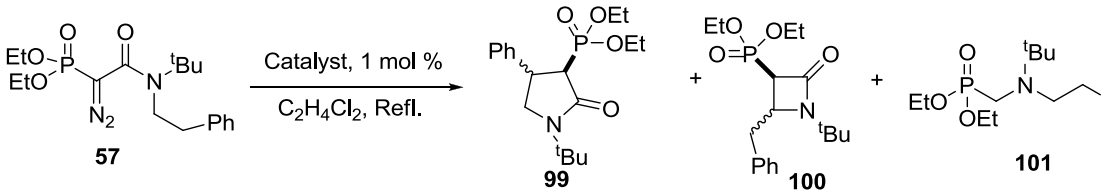
2.2.1.1. The α-substituent influence

This study was initiated with the decomposition of substrate **57** with several catalysts (Scheme 44):



35 $Rh_2(cap)_4$ **102** $Rh_2(tfa)_4$ **88** $Rh_2(OAc)_4(IPr)$ **89** $Rh_2(OAc)_4(SIPr)$

Scheme 43: Structure of selected catalysts.



Entry	Catalyst	t (h)	99 (%)[a]	*cis/trans*	100 (%)[a]	*cis/trans*	101 (%)[a]
1	$Rh_2(OAc)_4$ **1** [41]	4	91 (81)	0.06/1	5	2.1/1	-
2	$Rh_2(tfa)_4$ **102**	12	82 (66)	0.02/1	11 (10)	3.9/1	-
3	$Rh_2(cap)_4$ **35**	7	80 (76)	0.09/1	3 (3)	2.3/1	<2 (0)
4	$Rh_2(OAc)_4$(IPr) **88**	46	60 (56)	0.07/1	9 (7)	2.7/1	25 (23)
5	$Rh_2(OAc)_4$(SIPr) **89**	24	79 (66)	0.06/1	8 (7)	2.6/1	9 (9)

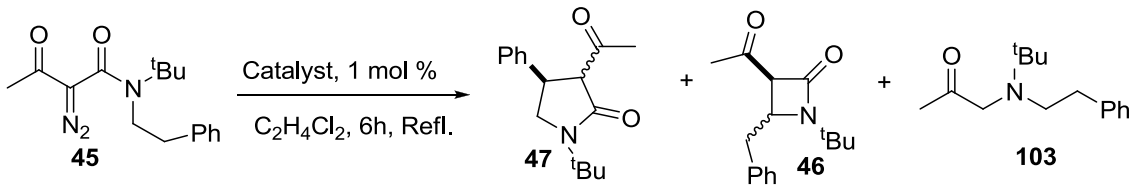
[a] Conversions obtained with ^{13}P NMR, in brackets are the isolated yields.

Scheme 44: Obtained results on the decomposition of **57** with several catalysts.

The decomposition of **57** with catalyst $Rh_2(OAc)_4$ is very selective for the formation of **99** though **100** is also obtained in 5 % yield. Among the studied catalysts $Rh_2(tfa)_4$ is the most electrophilic and β-lactam **100** was obtained in 10 % yield. $Rh_2(cap)_4$ is the less electronactractor catalyst and as expected it produces less amount of **100**. While the β-lactam is formed through a 5-membered ring transition state the γ-lactam is by a 6-membered ring one, where the metal carbenoid is more stable due to the electrondonating capabilities of the catalyst. The catalysts with the axial NHC take longer times for the reaction completion, being the $Rh_2(OAc)_4$(IPr) more unreactive for this reaction. Less γ-lactam **99** was obtained with both catalysts **88** and **89** when compared with $Rh_2(OAc)_4$. Besides the regular products, the reactions with these catalysts afford a new product **101** where a decarbonylation occurred. With $Rh_2(OAc)_4$(IPr) **88** complex, the product **101** raised to 25 %, while with $Rh_2(OAc)_4$(SIPr) **89** only gave 9 %. This product was also present with $Rh_2(cap)_4$ on a

vestigial amount (2 %), not isolated and only verified due to high sensitivity of ^{31}P NMR. Compound **101** is an unusual product since it may be originated via the Wolff rearrangement. The reaction diastereoselectivity was also observed due to the ^{13}P NMR. The $Rh_2(tfa)_4$ is the most selective for *trans* isomer of **99** and to the *cis* of **100**. $Rh_2(OAc)_4$ is the less selective for **99**. $Rh_2(OAc)_4(SIPr)$ and $Rh_2(OAc)_4(IPr)$ have intermediate diastereoselectivities for both lactams.

With acetyl as α-substituent the results are reported below (Scheme 45).



Entry	Catalyst	47 (%) [a]	46 (%) [a]	103 (%) [a]
1 [b]	$Rh_2(OAc)_4$ **1**	65 (47)	34 (25)	-
2 [b]	$Rh_2(OAc)_4(SIPr)$ **89**	32 (18)	39 (14)	29 (0)
3 [b]	$Rh_2(OAc)_4(IPr)$ **88**	18 (17)	46 (35)	36 (7)
4 [c]	$Rh_2(OAc)_4(IPr)$ **88**	23 (0)	46 (0)	31 (17)

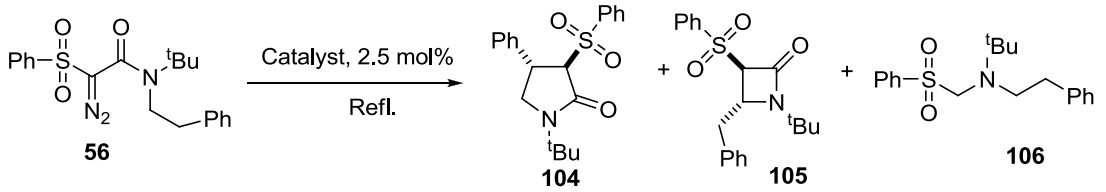
[a]Conversions obtained with ^1H NMR, in brackets are the isolated yields; [b]Isolated from silica chromatography

[c]Isolated from alumina chromatography

Scheme 45: Obtained results on the decomposition of **45**.

The reaction of **45** with $Rh_2(OAc)_4$ affords **47** in 65% conversion and **46** in 34% where no CO extrusion product was detected. With catalysts $Rh_2(OAc)_4$-NHC the reaction was complete during the same period of time and the CO extrusion product **103** was once more obtained. Catalysts with NHCs has different selectivities from each other and from $Rh_2(OAc)_4$. While $Rh_2(OAc)_4$ has a preference for **47** formation, catalyst $Rh_2(OAc)_4(SIPr)$ forms **47** and **46** in almost equal amounts. On the other hand, catalyst $Rh_2(OAc)_4(IPr)$ is far more selective towards β-lactam **46** formation, with CO extrusion product **103** alongside. Once more this CO extrusion product is not described in literature for those substrates and may be obtained by the Wolff rearrangement. The isolation of this product only was possible from alumina chromatography since in silica **47** and **103** have close retardation factors. On a similar experiment catalyst **89** was recovered in 56 % yield form the reaction mixture, where the remaining catalyst probably decomposed during the isolation.

Substrate **56** containing the phenylsulfonyl group as α-substituent, while maintain the remaining groups was tested. The obtained results are presented on Scheme 46.



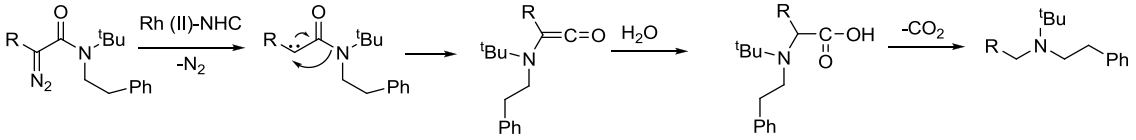
Entry	Catalyst	Conditions	104 (%)[a]	105 (%)[a]	106 (%)[a]
1	$Rh_2(OAc)_4$ **1**[42]	12 h, CH_2Cl_2	(95)	-	-
2	$Rh_2(OAc)_4$(SIPr) **89**	4 h, $C_2H_4Cl_2$	64 (54)	30 (21)	n. o.
3	$Rh_2(OAc)_4$(SIPr) **89**	53 h, CH_2Cl_2	89 (67)	8 (5)	n. o.
4	$Rh_2(OAc)_4$(IPr) **88**	53 h, CH_2Cl_2	(70)	(12)	n. o.

[a]Conversions obtained with ^{1}H NMR, in brackets are the isolated yields; n.o. = not obtained

Scheme 46: Obtained results on the decomposition of **56**.

The $Rh_2(OAc)_4$ decomposition of **56** is described in 2.5 mol % catalyst loading in refluxing CH_2Cl_2. Therefore the catalysts $Rh_2(OAc)_4$-NHC were tested under the same conditions for comparison purpose. The decomposition of substrate **56** is completed in 12 h. Under the same conditions catalysts $Rh_2(OAc)_4$-NHC require 53 h and no CO extrusion product **106** was observed. $Rh_2(OAc)_4$ only yields γ-lactam **104** while for $Rh_2(OAc)_4$-NHC catalysts the β-lactam **105** is also formed. $Rh_2(OAc)_4$(IPr) is the catalyst which affords more of **105**, under these conditions. The reaction in refluxing $C_2H_4Cl_2$ catalyzed by $Rh_2(OAc)_4$(SIPr) only takes 4 h and the β-lactam **105** is formed in an appreciable yield, but no CO extrusion product **106** was detected.

The α-substituent plays an important role on metal carbenoid stabilization due to electronic effects. The catalysts $Rh_2(OAc)_4$-NHC can only induce electronic effects on the reaction pathway since the NHC ligand is on one side and the reaction occurs with the opposite Rh center. Longer reaction times (24 to 53 h) were observed with phosphoryl **57 (**Scheme 44**)** and phenylsulfonyl **56** (Scheme 46) substituents and a lower time (6h) was required with the acetyl **45 (**Scheme 45**)** which can be explained since this is the most reactive substituent within these substrates. A new product is formed possibly via the Wolff rearrangement followed by water attack during the workup and further decarboxylation:

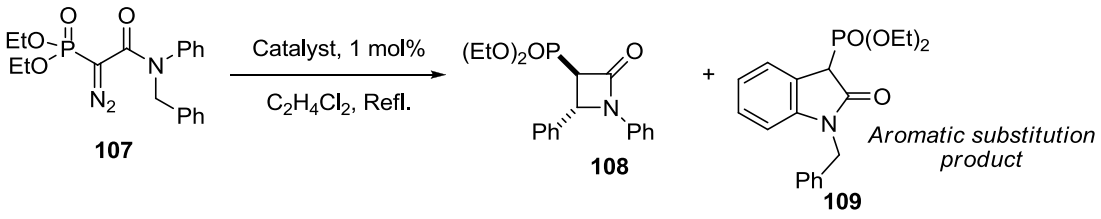


Scheme 47: A plausible mechanism for products **101** and **103** formation *via* Wolff rearrangement.

On the three cases β-lactam formation is observed with $Rh_2(OAc)_4$-NHC in a higher yield or as a new product, suggesting that theses catalysts have a preference for an early transition state. β-lactams and CO extrusion products were obtained in higher yields for $Rh_2(OAc)_4$(IPr) **88** therefore this catalyst shows a more different behavior than $Rh_2(OAc)_4$(SIPr) **89**, when compared to $Rh_2(OAc)_4$. On decomposition of **57** with $Rh_2(cap)_4$, having this catalyst less electronattractor ligands, **101** was detected in <2% conversion and with $Rh_2(tfa)_4$ a higher amount of β-lactam **100** was obtained which appears to imply that the axial coordination has different impact compared to the equatorial one.

2.2.1.2. The influence of the insertion center

To study the influence of the insertion center the α-substituents phosphoryl and ester were employed.

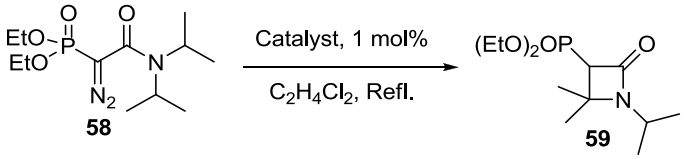


Entry	Catalyst	t (h)	108 (%)[a]	*cis / trans*	109 (%)[a]
1	$Rh_2(OAc)_4$ **1**[54]	24	12	0 / 1	83
2	$Rh_2(OAc)_4$(SIPr) **89**	53	12 (12)	0 / 1	85 (76)
3	$Rh_2(OAc)_4$(IPr) **88**	53	7 (6)	0 / 1	90 (80)

[a] Conversions obtained with ^{13}P NMR, in brackets are the isolated yields

Scheme 48: Obtained results on the decomposition of **107**.

The decomposition of **107** (Scheme 48) can afford the C-H insertion product **108** or the aromatic substitution **109**. The purification was only performed through celite filtration since **109** decomposes in alumina and **108** in silica. Again the $Rh_2(OAc)_4$-NHC catalysts require longer reaction time but provide similar selectivity to $Rh_2(OAc)_4$.



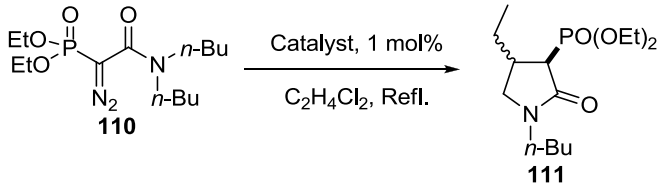
58 59

Entry	Catalyst	t (h)	59 (%)[a]
1	$Rh_2(OAc)_4$ **1**[41]	7	99 (88)
2	$Rh_2(OAc)_4$(SIPr) **89**	21	88 (80)

[a] Conversions obtained with ^{13}P NMR, in brackets are the isolated yields

Scheme 49: Obtained results on the decomposition of **58**.

The decomposition of **58** (Scheme 49) occurs with $Rh_2(OAc)_4$ in 7 h. With $Rh_2(OAc)_4$(SIPr) it takes 21 h and the yield of **59** is inferior to the one obtained for $Rh_2(OAc)_4$ (88 vs 99 %).



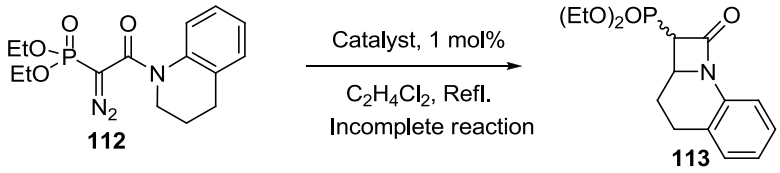
110 111

Entry	Catalyst	t (h)	111 (%)[a]	*cis / trans*
1	$Rh_2(OAc)_4$ **1**[41]	2	92 (87)	0.08 / 1
2	$Rh_2(OAc)_4$(SIPr) **89**	16	93 (89)	0.07 / 1

[a] Conversions obtained with ^{13}P NMR, in brackets are the isolated yields

Scheme 50: Obtained results on the decomposition of **110**.

The decomposition of **110** (Scheme 50) occurs with $Rh_2(OAc)_4$ in 2h. With $Rh_2(OAc)_4$(SIPr) it takes 16 h, the yield and diastereoselectivity are similar.



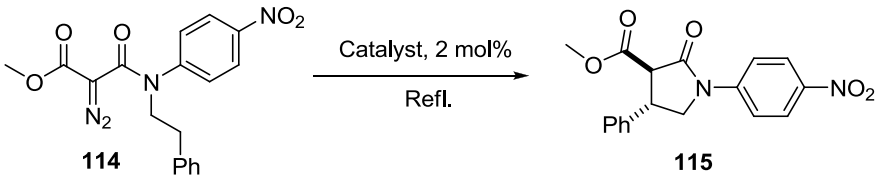
112 113

Entry	Catalyst	t (h)	112 (%)[a]	113 (%)[a]
1	$Rh_2(OAc)_4$ **1**[41]	4	-	(73)
2	$Rh_2(OAc)_4$(SIPr) **89**	70	48 (41)	47 (41)

[a] Conversions obtained with ^{13}P NMR, in brackets are the isolated yields

Scheme 51: Obtained results on the decomposition of **112**.

The reaction of **112** (Scheme 51) is complete in 4 h in refluxing $C_2H_4Cl_2$. With $Rh_2(OAc)_4$(SIPr) in 70 h 41 % of the reagent still remains and other 41 % of product **113** is obtained. Perhaps the reaction is much slower due to the cyclic N-substituent.



114 **115**

Entry	Catalyst	Conditions	115 (%)[a]
1	$Rh_2(OAc)_4$ **1**	CH_2Cl_2, 7 h	(98)
2	$Rh_2(OAc)_4$(SIPr) **89**	$C_2H_4Cl_2$, 24 h	(98)

[a] In brackets are the isolated yields

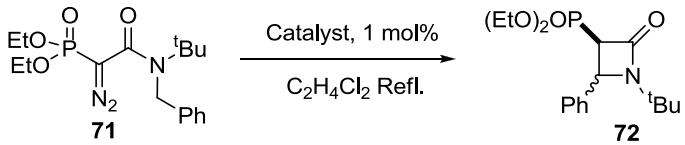
Scheme 52: Obtained results on the decomposition of **114**.

Catalyst $Rh_2(OAc)_4$ requires 7 h to complete the cyclization of **114** (Scheme 52) in CH_2Cl_2. $Rh_2(OAc)_4$(SIPr) requires 24 h despite the superior boiling point of the solvent used and no β-lactam was observed. Nevertheless identical yields were obtained.

The obtained results indicate that the effect of the NHC mono coordinated on $Rh_2(OAc)_4$ doesn't play a important role on selectivity regarding the insertion center. As well as the previous study longer reaction times were required.

2.2.1.3. The influence of the N-substituents, the insertion center and mechanistic studies

The N-substituent has an important role on reaction chemoselectivity since the conformational effects caused during the C-H insertion. Therefore the effect of this substituent was also evaluated. The *tert*-butyl group was chosen due to its bulkiness.



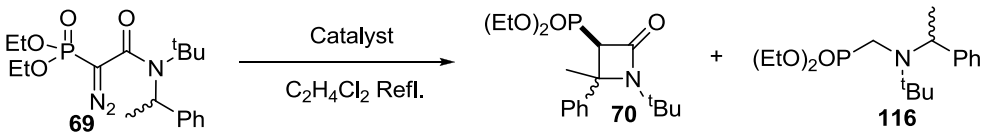
71 **72**

Entry	Catalyst	t (h)	72 (%)[a]	*cis /trans*
1	$Rh_2(OAc)_4$ **1**[41]	7	(89)	1 /0.40
2	$Rh_2(OAc)_4$(SIPr) **89**	47	87 (84)	1/ 0.22

[a] Conversions obtained with ^{13}P NMR, in brackets are the isolated yields

Scheme 53: Obtained results on the decomposition of **71**.

The reaction of **71** (Scheme 53) with $Rh_2(OAc)_4$ requires 7 h, under the same conditions $Rh_2(OAc)_4$(SIPr) requires 47 h and the decarbonylation product is not obtained.

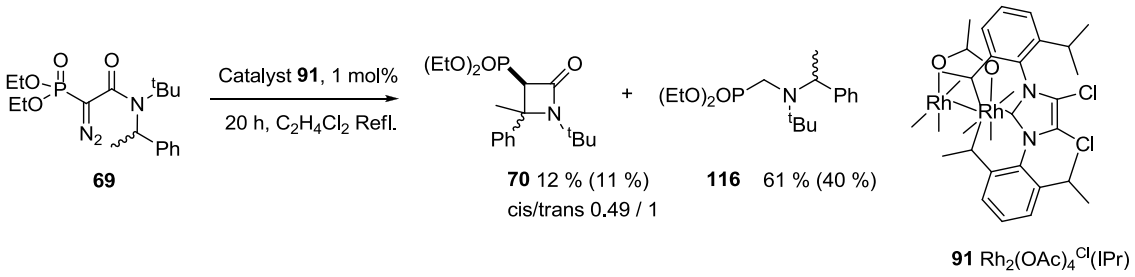


Entry	Catalyst (eq.)	t (h)	70 (%)[a]	*cis* / *trans*	116 (%)[a]
1	$Rh_2(OAc)_4$ **1** (1) [41]	4	(75)	1.5 / 1	-
2	$Rh_2(OAc)_4$(SIPr) **89** (1)	25	23 (17)	0.63 / 1	51 (44)
3	$Rh_2(OAc)_4$(IPr) **88** (1)	25	19 (15)	0.44 /1	57 (47)
4	$Rh_2(OAc)_4$(IPr) **88** (2) + $Rh_2(OAc)$ **1** (2)	3	72 (56)	1.38 /1	18 (13)
5	No catalyst	25	33	0.31 / 1	17

[a] Conversions obtained with ^{13}P NMR, in brackets are the isolated yields

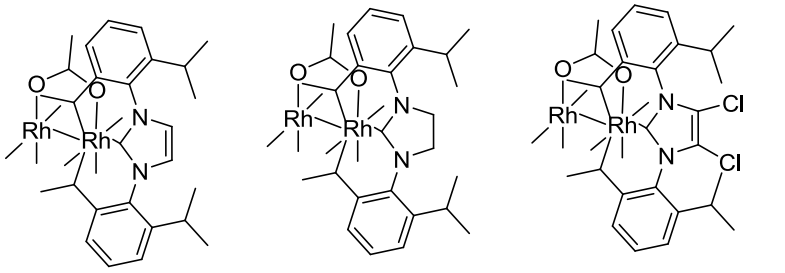
Scheme 54: Obtained results on the decomposition of **69**.

Catalyst $Rh_2(OAc)_4$ decomposes **69** (Scheme 54) in 4 h with β-lactam formation in 75 % and without CO extrusion product **116**. Both catalysts $Rh_2(OAc)_4$-NHC **88** and **89** require 25 h for substrate decomposition and the CO extrusion product is again obtained. When $Rh_2(OAc)_4$(IPr) **88** was employed the CO extrusion product was obtained in 57 % conversion, modifying the reaction selectivity. A experiment where both $Rh_2(OAc)_4$(IPr) and $Rh_2(OAc)_4$ are used still results on **116** formation albeit in 18 % conversion, demonstrating that even though its diminished electrophilicity, $Rh_2(OAc)_4$(IPr) can still compete for the substrate. A control experiment without catalyst afforded a complex mixture with 33% of β-lactam **70**, 17 % of CO extrusion product **116** and 4 % of unreacted substrate **69**. Here the CO extrusion product probably arises from the thermal induced Wolff rearrangement followed by water attack during the workup and decarboxylation (Scheme 47).



Scheme 55: Obtained results on the decomposition of **69** with **91**. Conversions obtained with ^{13}P NMR, in brackets are the isolated yields.

For this specific reaction catalyst **91** was used (Scheme 55). This differs from usual catalyst $Rh_2(OAc)_4(IPr)$ **88** by the chlorinated backbone. The decomposition of substrate **69** with this catalyst affords the CO extrusion product **116** in the best conversion obtained, 61 %, where the inductive chlorine effect is responsible for this reactivity modification.



88 $Rh_2(OAc)_4(IPr)$ **89** $Rh_2(OAc)_4(SIPr)$ **91** $Rh_2(OAc)_4^{Cl}(IPr)$

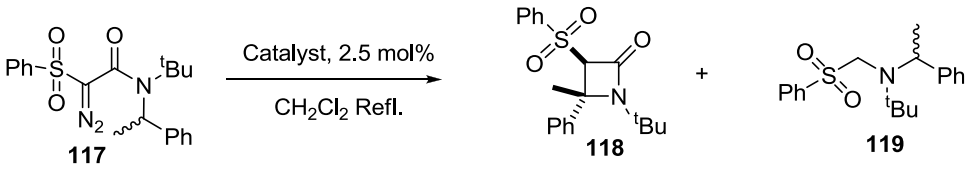
Entry[a]	Catalyst	d_{Rh-Rh} (Å)	WI_{Rh-Rh}	$d_{C(NHC)-Rh}$ (Å)	$WI_{C(NHC)-Rh}$
1	$Rh_2(OAc)_4$ **1**	2.39	0.79	-	-
2	$Rh_2(tfa)_4$ **102**	2.39	0.80	-	-
3	$Rh_2(cap)_4$ **35**	2.39	0.76	-	-
4	$Rh_2(OAc)_4(IPr)$ **88**	2.46	0.54	2.17	0.38
5	$Rh_2(OAc)_4(SIPr)$ **89**	2.46	0.54	2.18	0.38
6	$Rh_2(OAc)_4^{Cl}(IPr)$ **91**	2.45	0.56	2.20	0.35

[a] DFT calculations performed at the B3LYP/631LAN level of theory [b] WI= Wiberg Index

Scheme 56: DFT calculated data for dirhodium (II) complexes.

DFT calculations were kindly performed by Prof. Luís F. Veiros (IST) on a collaborative base. Catalysts structures displayed on Scheme 56 were optimized and the data obtained shows a weaker Rh-Rh bond strength on dirhodium (II)-NHC catalysts

(WI[1]=0.54-0.56 *vs* 0.76-0.80). Catalyst $Rh_2(OAc)_4^{Cl}$(IPr) is the best one to induce the decarbonylation product **116**, it is also the one with lowest NHC-Rh Wiberg index, though no trend is observed alongside other catalysts.

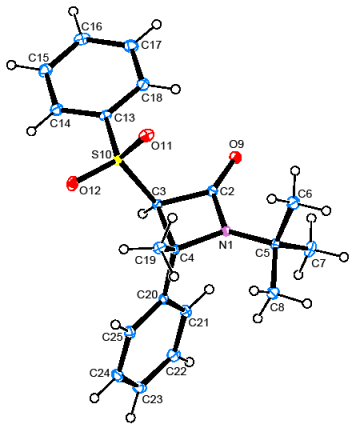


Entry	Catalyst (eq.)	t (h)	(%)[a]	(%)[a]
1	$Rh_2(OAc)_4$ **1**	2.5	39 (33)	n.o.
2	$Rh_2(OAc)_4$(SIPr) **89**	120	60 (52)	n.o.
3	$Rh_2(OAc)_4$(IPr) **88**	120	60 (51)	n.o.

[a]Conversions obtained with ^{1}H NMR, in brackets are the isolated yields; n.o. = not obtained

Scheme 57: Obtained results on the decomposition of **117**.

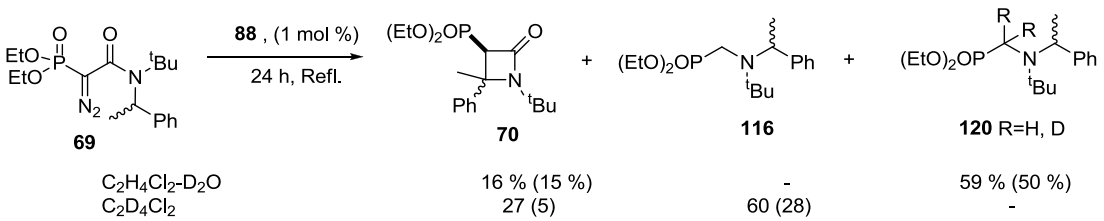
The phenylsulfonyl analogue of substrate **69** was synthesized (substrate **117**) in order to determine if the N-substituents could have a determining influence on rendering compound **119** (Scheme 57). Though the reaction time with catalysts $Rh_2(OAc)_4$-NHC is much longer, β-lactam **118** is formed in better yield than $Rh_2(OAc)_4$ and no CO extrusion product **119** is detected. The relative stereochemistry of the quaternary stereocenter of **118** was determined as *trans* by single crystal X-ray diffraction (Scheme 58).



Scheme 58: X-ray diffraction image of **118**.

[1] Wiberg indices are electronic parameters that are related to the electron density between atoms. They can be obtained from a natural population analysis and provide an indication of the bond strength.

To verify if the CO extrusion compound **116** is obtained by Wolff rearrangement followed by water attack and decarboxylation (Scheme 47), the reaction was performed in $C_2H_4Cl_2$ saturated with deuterium oxide (Scheme 59). Indeed deuterium incorporation was observed on product **120**. A blank with the deuterated solvent $C_2D_4Cl_2$ didn't afforded the deuterated product **120**, but **116** instead. Additionally no deuteride incorporation was observed on standing the amine **116** in a 2.3:1 mixture of tetrahydrofuran and D_2O at 55º C for 27 h. These results support that a Wolff rearrangement may be responsible for the CO extrusion products.



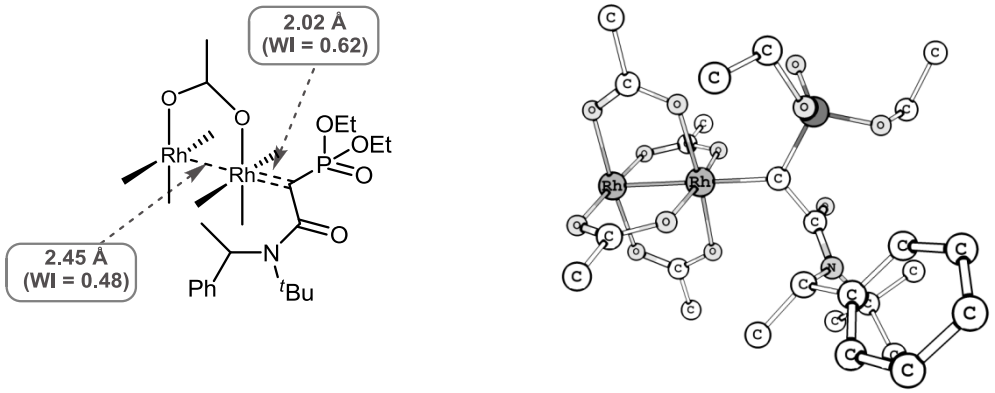
Scheme 59: Decomposition of substrate **69** with $Rh_2(OAc)_4(IPr)$ in deuterated solvents. Conversions obtained with ^{13}P NMR, in brackets are the isolated yields.

2.2.1.4. Computational studies on the reaction mechanism

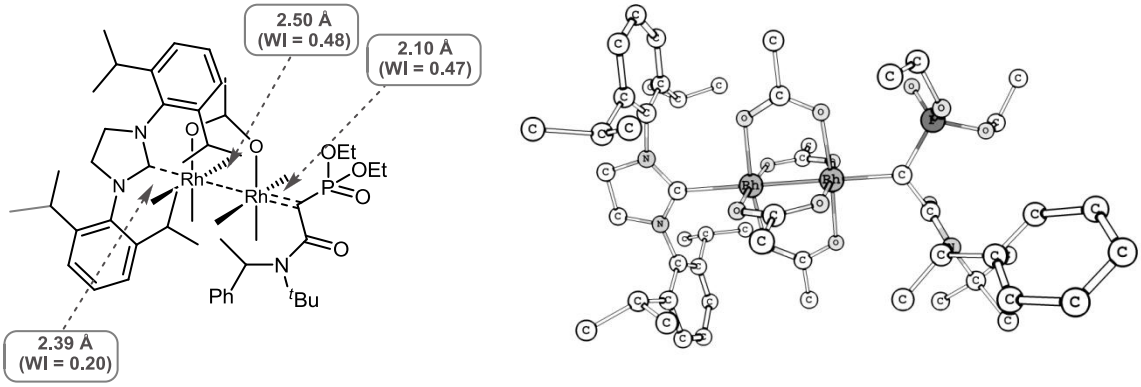
By taking these several effects in consideration perhaps it may be hypothesized that the presence of a *s*-donating NHC ligand on the axial position can weaker the bond between the carbenoid and the terminal Rh center. As stated before DFT calculations were kindly performed by Professor Luís F. Veiros. The calculations were made using the Gaussian 98 software package[56], and the B3LYP hybrid functional, without symmetry constraints. That functional includes a mixture of Hartree-Fock exchange with DFT exchange-correlation. The LanL2DZ basis set augmented with a f-polarization function was used for Rh, and a standard 6-31G(d,p) for the remaining elements. A Natural Population Analysis (NPA) and the resulting Wiberg indices were used for a detailed study of the electronic structure and bonding of the optimized species. The nature of stationary points was checked by frequency calculation, yielding no imaginary points for the minima.

Indeed the DFT calculations with substrate **69** revel a Rh- transient carbenoid bond extension of 0.8 Å on the $Rh_2(OAc)_4(SIPr)$ complex compared to $Rh_2(OAc)_4$ (Scheme

60 and Scheme 61). The Rh-Rh bond also suffer a stretching. According to Nakamura's *et al.*[23] calculations the Rh-Rh bond breaks completely during the metal carbenoid formation. With our calculations the Rh-Rh bond only weakens since a Wiberg index of 0.48 was obtained for this transient specie.

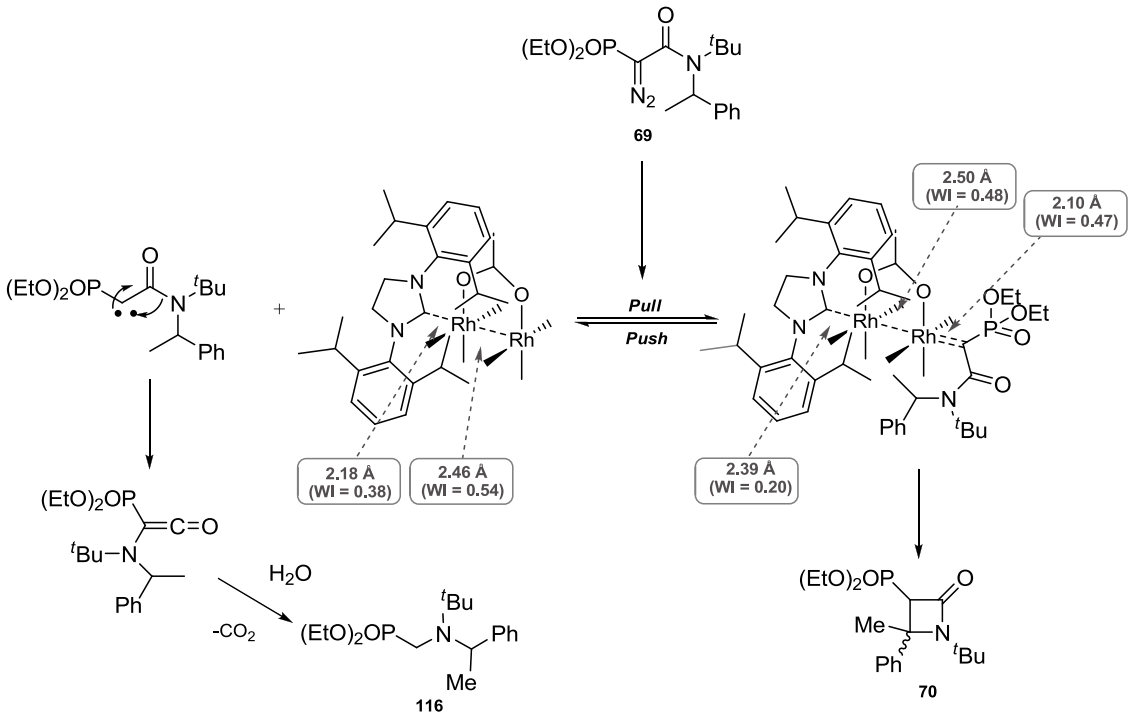


Scheme 60: Optimized structure by DFT for the reaction of $Rh_2(OAc)_4$ with substrate **69** (H omitted).



Scheme 61: Optimized structure by DFT for the reaction of $Rh_2(OAc)_4$(SIPr) with substrate **69** (H omitted).

A push-pull mechanism can be in operation for this reaction (Scheme 62). The dinitrogen liberation and carbenoid formation weakens the Rh-NHC bond (*pull*), though its integrity is secured by the stereo protection conferred by the bulky structure of the NHC. On the other end, the NHC also weakens the metal carbenoid bond (push) which in combination with stereo-effects exerted by the acetamide structure may lead to the generation of a free carbene type intermediate which undergoes a typical Wolff rearrangement forming the decarbonylated product which can become the main reaction pathway. The remaining acetamide bonded to the Rh center may follow the regular C-H insertion mechanism.

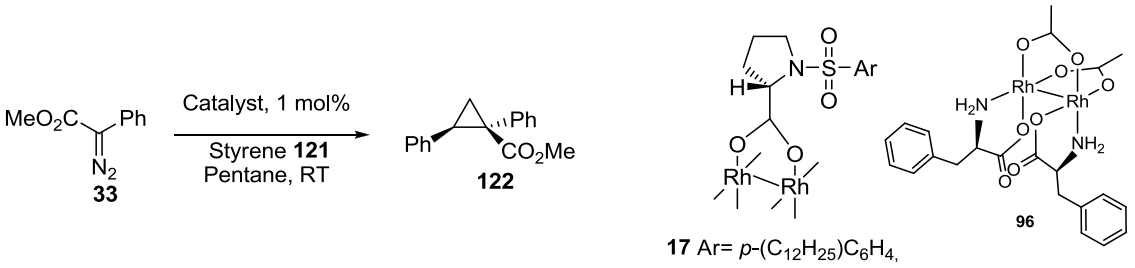


Scheme 62: Relevant structural and electronic parameters calculated for the metal carbenoid and NHC-metal carbenoid derived from diazo compound **69**.

2.2.2. Study of Catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$

Catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** was developed by this laboratory for asymmetric C-H insertions using water as solvent[55]. Since reactions with dirhodium (II) carbenoids are very dependent of the catalyst structure as well as substrate structure[4a], other known reactions were performed to check the catalyst compatibility.

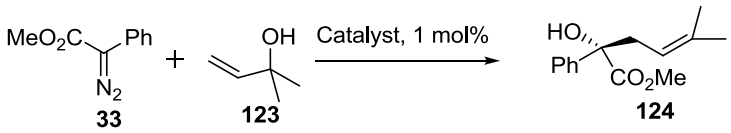
The intermolecular cyclopropanation[57] of olefins was selected since it's a well established method which takes advantage of dirhodium (II) carbenoids. A substrate of type III was selected to add motif variation. The cyclopropanation between diazo **33** and styrene **121** was carried out for both catalysts but while the catalyst Rh_2(*S*-DOSP)$_4$ **17** afforded the product in 90% yield and 87% *ee*[58], the catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** achieved 64% yield (Scheme 63):



Entry	Catalyst	t(h)	122 (%)	*ee*(%)
1	Rh_2(*S*-DOSP)$_4$ **17**[59]	–	90	87
2	$Rh_2(OAc)_2$(*S*-Phe)$_2$ **96**	20	64	-

Scheme 63: Cyclopropanation between **33** and styrene **121**.

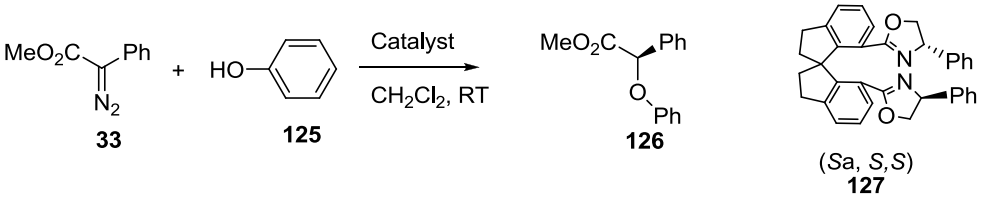
Next the ROH insertion / [2,3] sigmatropic rearrangement between substrate **33** and the alcohol **123** was tested (Scheme 13, up). The catalyst Rh_2(*S*-DOSP)$_4$ provides **124** with 40% yield and 79% *ee* in pentane at RT[59], the catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** only at refluxing hexane provides **124**, but only in 22% yield and 23% *ee* (Scheme 64):



Entry	Catalyst	Conditions	124 (%)	*ee*(%)
1	Rh_2(*S*-DOSP)$_4$ **17**	Pentane, RT, 2h	40	79
2	$Rh_2(OAc)_2$(*S*-Phe)$_2$ **96**	Hexane, Reflux 22h	22	23

Scheme 64: Rh (II)-catalyzed ROH insertion/[2,3] sigmatropic rearrangement between **33** and **123**.

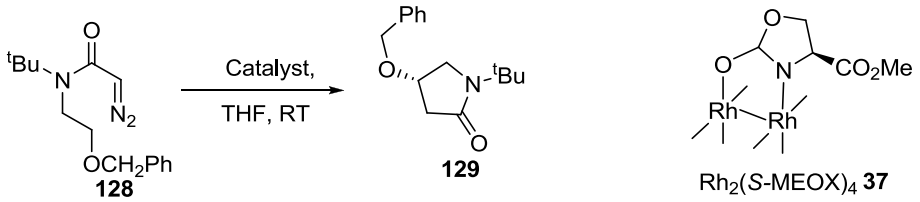
The ArOH insertion was also tested. Cu-based catalysts gave better *ee*'s with this particular reaction and catalyst CuCl / **127** provides the product with 71% yield and only 10% *ee*[60]. The catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** provides the product with 65% yield but no *ee* was observed (Scheme 65):



Entry	Catalyst	t(h)	126 (%)	*ee*(%)
1	CuCl / **127**[60]	3	71	10
2	$Rh_2(OAc)_2$(*S*-Phe)$_2$ **96**	1	65	-

Scheme 65: PhOH insertion with **33**.

The intramolecular cyclization of a type I diazo compound was performed. The reaction of **128** with catalyst Rh_2(*S*-MEOX)$_4$ **37** affords the γ-lactam **129** in 90% yield and 91% *ee*[61]. On the other hand, the catalyst **96** gave 76% yield but no *ee* was again observed (Scheme 66):



Entry	Catalyst	t (h)	129 (%)	*ee*(%)
1	Rh_2(*S*-MEOX)$_4$ **37**[61]	0.5	90	91
2	$Rh_2(OAc)_2$(*S*-Phe)$_2$ **96**	2	76	-

Scheme 66: Intramolecular cyclization of **128**.

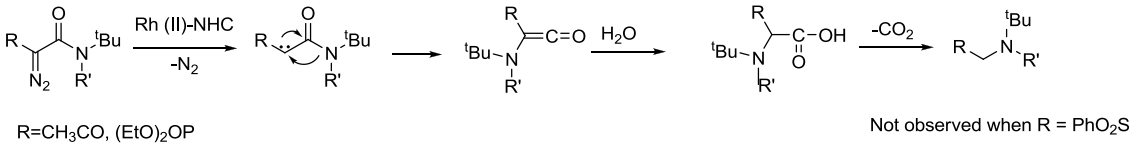
Since the majority of studied reactions didn't afford *ee* and only product **124** was obtained in 23% which is less than the 79% *ee* obtained with Rh_2(*S*-DOSP)$_4$, catalyst, $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** it is not the best choice for the studied reactions. Since the best result was obtained with the already known two electronattractor diazo substituents (Scheme 42), this catalyst **96** is most suited for this diazo compounds type, rather other two (types I and III). The reactions weren't conducted in water but in the preferential solvent for the best *ee* provided by the reported catalyst. Furthermore it's not expected significative *ee* improvements by performing the reaction in water.

2.3. Conclusions

The previously reported catalyst **80** was not stable under catalytic diazo decomposition for C-H insertion and alkynes cyclization. All gathered information about our $Rh_2(OAc)_4$-NHC catalysts suggest that the catalysts are stable under the tested reactions. The $Rh_2(OAc)_4$(SIPr) **89** is stable under refluxing 1,2-dichloroethane for 24 h; all the reactions maintained the characteristic wine color of the catalyst, even the most prolonged ones; the catalyst was isolated from the a reaction mixture in 56 % yield, where the remaining catalyst probably decomposed during the isolation. The selectivity on an thermal diazo decomposition was different favoring the C-H insertion product **70** where the catalysts $Rh_2(OAc)_4$-NHC favor the decarbonylation product **116** and the selectivity of a reaction carried in 1,2-dichloroethane saturated with D_2O was the same. If the D_2O had decomposed the dirhodium (II)-NHC bond the free $Rh_2(OAc)_4$ would catalyze the reaction since it is known that this catalyst is active in water also.

All the reactions carried with $Rh_2(OAc)_4$-NHC catalysts required more time to reaction completion[49, 62] (except with the acetyl α-substituent, Scheme 45). These complexes have increased electron density at the free Rh center which can decrease the diazo compound tendency for the nucleophilic attack.

The decarbonylation product was obtained for several substrates. This transformation may occur *via* a Wolff a mechanism which is not described in the literature for those substrates and a reaction with both catalysts $Rh_2(OAc)_4$(IPr) and $Rh_2(OAc)_4$ afforded this product. Therefore $Rh_2(OAc)_4$(IPr) can compete for the substrate despite its reduced reactivity. This compound can be obtained via Wolff rearrangement followed by water attack on the ketene and by decarboxylation (Scheme 67). The deuterated decarbonylated product **120** supports this mechanism. The bulky N-substituents and the α-substituents play a decisive role on this reaction pathway and the axial position appears to induce a different reactivity than equatorial ones.



Scheme 67: Proposed mechanism for the decarbonylated product.

Often across this study catalyst $Rh_2(OAc)_4$(IPr) afforded more β-lactam product or more CO extrusion product than $Rh_2(OAc)_4$(SIPr). The only structural distinction between these catalysts is the NHC imidazole backbone which is unsaturated on $Rh_2(OAc)_4$(IPr), thereby the N σ donation is spread between the C carbene and the π bond and the NHC's σ donating character is lower than $Rh_2(OAc)_4$(SIPr). This subtle electronic effect is responsible for the different reactivity and the inductive effect caused by Cl on $Rh_2(OAc)_4^{Cl}$(IPr) is also responsible for the tuning since the reaction occurs on one axial position and the NHC is coordinated on the other.

Catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ is better suited for type II diazo substrates since the other types here tested afforded low *ee*.

3. DIAZO-FREE C-H INSERTION WITH C-C BOND FORMATION

Abstract:

The diazo compounds have potential explosive behavior which makes them unsuitable for large scale applications. Although they are routine laboratory reagents, the large advances on dirhodium (II) carbenoid chemistry especially on C-H insertion with C-C bond formation, haven´t found applications on industrial scale mainly due to this limitation. At the current stage the reported alternatives don't offer a suitable surrogate. Here several research lines were followed in order to address this problem, which culminated on a diazo and transition-metal free approach. A phenyliodonium ylide is generated and decomposed in situ to form the C-H insertion / C-C bond formation, β-lactam product via a free carbene, mechanistically supported both by experiments and DFT calculations.

Published articles *in peer* reviewed journals for this chapter:

- X. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros, N. Maulide*; *Angew. Chem. Int. Ed.*, **2012**, 51, 8886.

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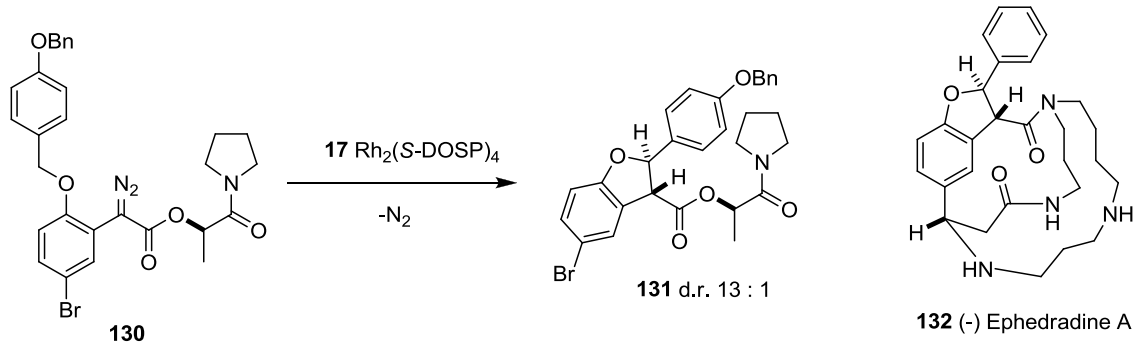
3.1. Introduction

3.1.1. General Considerations

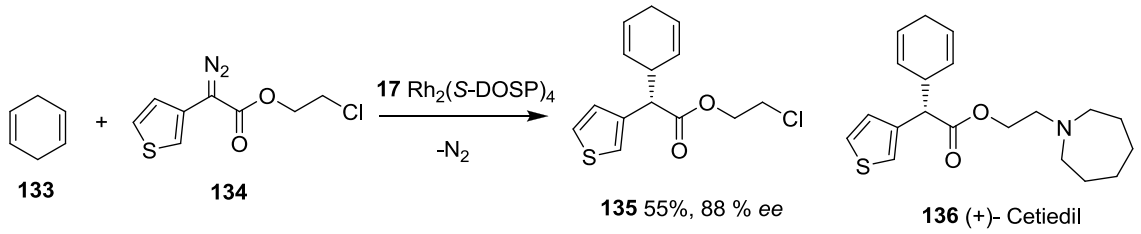
Diazo compounds are well established reagents in contemporary organic synthesis. They are the preferred reagent for metal carbenoid formation with dinitrogen liberation in a clean reaction. Metals such as Copper, Ruthenium, Palladium and specially Rhodium have being used for the diazo decomposition where they afford a highly reactive transient metal carbenoid intermediate which can undergo several synthetic useful transformations such as cyclopropanation with alkenes or cyclopropenation with alkynes; ylide transfer reactions with a nucleophilic heteroatoms such as ROH, RNH or RSH or even C-H insertion on sp^3 carbons which allow the funcionalization of unreactive bonds[15].

Dirhodium (II) complexes have been used as very efficient catalysts for diazo decomposition and can perform all above mentioned transformations including the C-H insertion. The other metals such as copper provide usually low yields on C-H insertion reactions but are suitable for cyclopropanation[63] / cyclopropenation[5] and ylide transfer; their lower price also makes them better candidates for these reactions. Nonetheless the dirhodium (II) high cost may not be a constraint since this catalyst has high activity and the C-H insertion can greatly shorten the synthesis of the target molecule where an otherwise unreactive C-H bond can be specifically activated. The predictable results of the match pair dirhodium (II) catalyst with diazo compounds enables new disconnection approaches and the pursuit of complex targets as it's the case of total synthesis of natural products. When chiral dirhodium (II) complexes are employed the reactions can achieve a pronounced enantioselectity. As an example, for the total synthesis of (-)-Ephedradine A[64] **132** (Scheme 68) the catalyst Rh_2(*S*-DOSP)$_4$ was employed on intramolecular C-H insertion where a chiral auxilary was responsible for the enantioinduction (13:1 diastereoselective ratio).



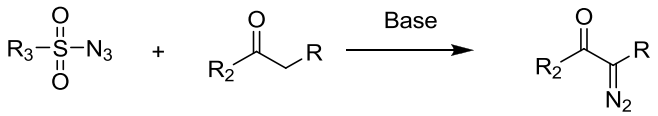
Scheme 68: Total synthesis of (-)-Ephedradine A.

On the synthesis of (+)-Cetiedil[65] **136** (Scheme 69) the same catalyst, Rh_2(*S*-DOSP)$_4$, was used for intermolecular C-H insertion providing 88 % *ee*.



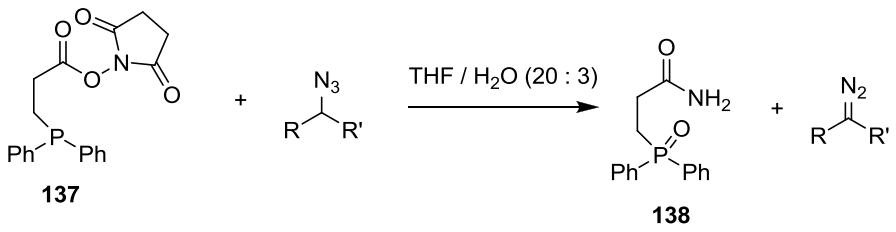
Scheme 69: Key step on the total synthesis of (+)-Cetiedil.

Diazo compounds are usually synthesized from sulfonyl azides which act as diazo transfer reagent (Scheme 70) under basic conditions.



Scheme 70: Synthesis of a diazo compound with a diazo transfer reagent.

Despite of the availability of several other methods for the diazo functionality synthesis, more efforts continue to be developed which shows how hard it is to access these valuable rhodium carbenoid precursors by other means. In 2009, a phosphine-mediated azide conversion into diazo compounds method was developed[66] (Scheme 71). Now the phosphine **137** is commercial available and the reaction was expanded to use water as sole solvent[67].



Scheme 71: A phosphine-mediated diazo synthesis.

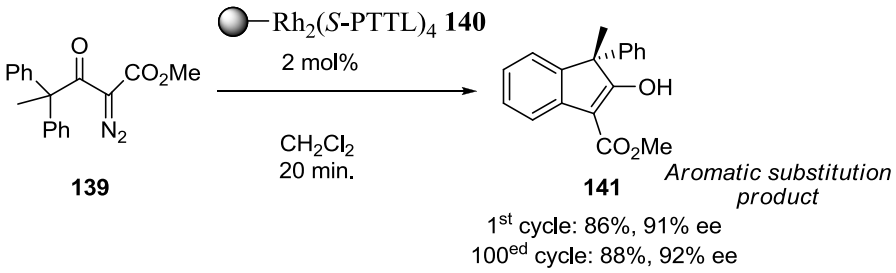
Despite of all the advantages offered by the pair dirhodium (II) / diazo compounds on C-H insertion, its use has much be confined to laboratories where the continuous research over the past twenty years has broader the applications of this set.

Despite many advantages, the diazo functional group also have some inherent drawbacks. The metal carbenoid formation occurs with dinitrogen extrusion which is a gaseous byproduct. It leaves the reaction mixture and because of its stability it doesn't take part on side reactions. The easy dinitrogen liberation and heat liberation usually occurs smoothly and on a predictable fashion and on laboratories it escapes to the atmosphere, maintaining the reaction vessel's pressure constant. On industrial scale applications though a single non controlled diazo reaction can cause an explosion, which is a risk that can't be afforded. Therefore the laboratorial *state of the art* has a gap with the potential industrial applications which is growing and more recently many efforts have been taking place to fill this gap. Besides their inherent explosive behavior diazo compounds are toxic and carcinogenic and even on small scales extra care is required on handling them.

The simplest diazo compound, the diazo methane, is gaseous and extremely shock sensitive[68] it is also a strong respiratory irritant agent that can cause asthmatic symptoms. Several violent explosions were also reported by contact of diazomethane with sharp surfaces. By introducing an electronwithdrawing group such as ester it becomes less hazardous not only due to the superior boiling point but also because of the stabilization by resonance. These diazo compounds are commercially available, but with special cautions: diazomethane is generated whenever necessary mainly *via* Diazald® reagent and the ethyl diazoacetate is sold in solution.

All these drawbacks make large scale applications prohibitive but also because the main diazo transfer reagent, the azide, is also potentially explosive. The large scale applications with rhodium are also extremely costly, despite the high benefits of the C-H insetion reaction. This problem can be circumvented by the catalyst recover. In 2011 Hashimoto *et al.* published[69] the reuse of the polymer supported catalyst Rh_2(*S*-PTTL)$_4$

140, where they achieved 100 sequential reaction cycles with residual rhodium leaching and without yield and enantioselectivity drop (Scheme 72).



Scheme 72: The reuse of a polymer supported dirhodium (II) catalyst.

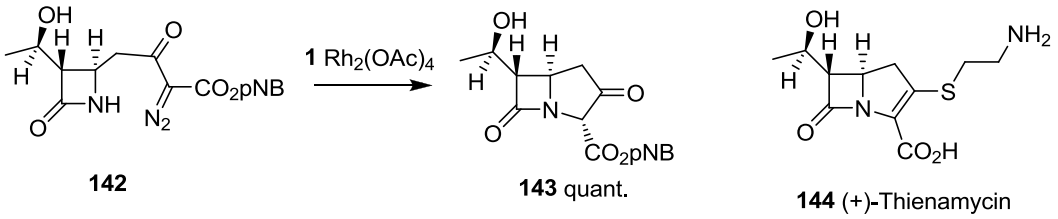
There are several previous reports on dirhodium (II) catalyst recycling[70] which shows the high cost of this precious metal can be circumvented, therefore the inertia to be adopted belongs to the diazo functional group and it's synthesis from azides. There is an example of a new diazo transfer agent synthesis based on the azide moiety, which was considered secure in the beginning[71] but after several experiments the authors experienced an explosion and then considered their already published methodology unsafe, which shows the unpredictability of the reagent.

There are some methodologies available which can partially solve the diazo problem is some extent, but so far none can be used as true diazo compounds surrogate and so the demand proceeds.

3.1.2. Industrial Scale Applications of Diazo Compounds

Even though the diazo's associated risks are often too dangerous to be taken, some industrial scale applications have been reported[72].

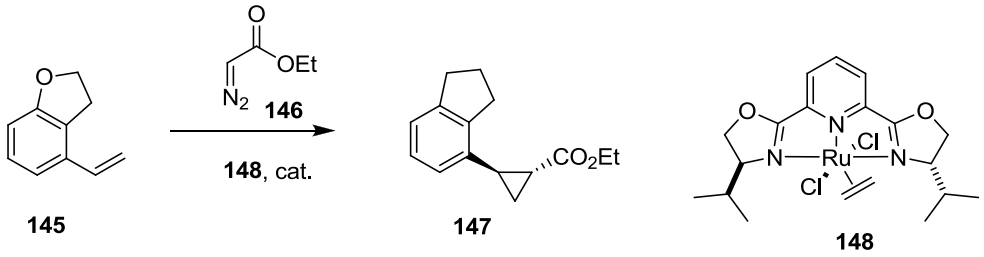
Among the scarce examples, available the synthesis of the carbapenem antibiotic (+)-thienamycin **144** is especially relevant. This antibiotic is still one of the most potent natural occurring ones and it displays excellent activity against both gram-positive and gram-negative bacteria and it is resistant to bacterial β-lactamases, besides its derivatives are also used to treat drug-resistant bacterial strains[73]. Its first total synthesis was performed by the Merck company in 1978[74] and the first asymmetric total synthesis was performed again in 1980 by Merck[75]. A dirhodium (II)-catalyzed diazo ecomposition with N-H insertion was used to perform the key step forming the second ring of this highly strained and reactive β-lactam (Scheme 73).



Scheme 73: Key step on the first asymmetric total synthesis of (+)-thienamycin, by Merck.

On a later report[76] (1999) the mentioned production scale for a derived carbapenem was 2.7 kg of diazo compound and 21.4 g, 0.5 mol % of another Rh(II)-based catalyst, showing the standing concern for this transformation.

Another reported industrial process uses ethyl diazoacetate **146** on an asymmetric olefin cyclopropanation with a chiral Ru-based catalyst[77]. Once synthesized this diazo reagent is kept in solution at 5 ± 5 º C and is added over 16 h to the olefin which reduces the explosion risks. The reaction was further scaled up to 50 Kg of substrate **145** on a pilot plant.



Scheme 74: Asymmetric cyclopropanation conducted on a pilot plant.

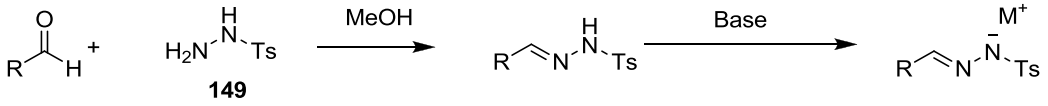
To avoid the diazo compounds hazards, many efforts are being conducted by both academia and industry. Some take advantage of the *in situ* generation of diazo compounds and others by replace it for another functional group.

3.1.3. *In Situ* Formation of Diazo Compounds

The *in situ* generation of diazo compounds doesn't avoid them but rather uses diazo precursors which are more stable than the free diazo compound. The diazo formation and the consequent dinitrogen liberation can be limited by catalyst amount.

Aggarwal's group developed a methodology which uses tosylhydrazone salts as a more stable diazo precursor[68, 78]. An aldehyde is reacted with *p*-tolylsulfonylhydrazide **149** and the sodium tosylhydrazone salt is formed by treating this precipitate with a base

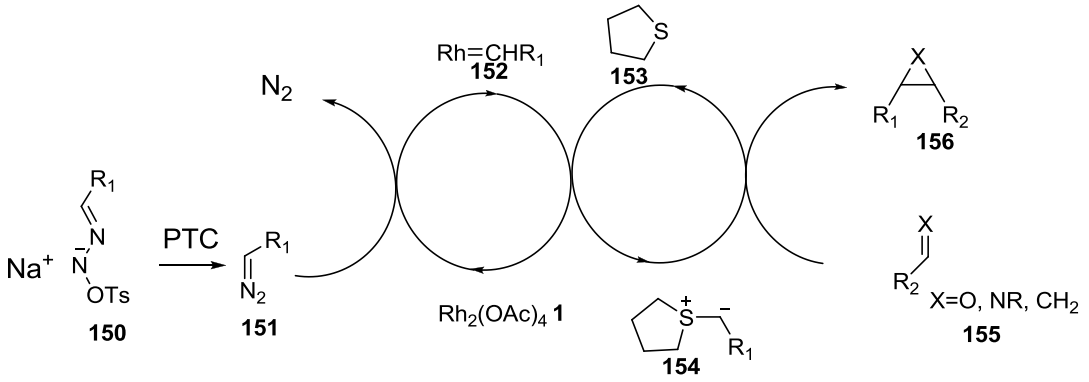
(Scheme 75). Different counter-ions were employed which provided better results depending on the reaction. In order to prevent thermal or photochemical decomposition, these diazo precursors were stored at -20 ºC. Electron rich tosylhydrazone salts could be stored without decomposition while electron poor ones needed to be prepared prior to use due to their instability. This offers a complementary solution to the synthesis of diazo compounds since they require an electronwithdrawing group to be handled safely in the laboratory.



Scheme 75: Preparation of tosylhydrazone salts.

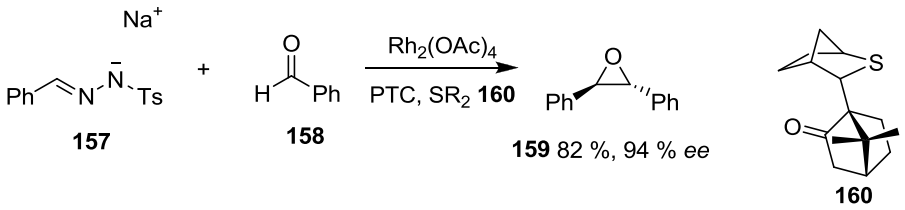
Tosylhydrazone salts are poorly soluble in common solvents so a phase transfer catalyst (PTC) was frequently employed: benzyltriethylammonium chloride was used with more polar solvents while less polar ones required a phase transfer catalyst such as tri-*n*-octylmethylammonium chloride (Aliquat® 336). The phase transfer catalyst also aided the decomposition of the salt into the active diazo compound. The reaction temperature range was 20 - 30º C depending on the stability of the salt.

The reaction mechanism is summarized on Scheme 76. The tosylhydrazone salt **150** solubilizes with the phase transfer catalyst and generates the diazo compound **151** *in situ*, the diazo reacts with the dirhodium (II) catalyst affording the highly reactive metal carbenoid **152** which is attacked by the sulfide **153** where the sulfur ylide **154** is formed, this ylide is then traped by the aldehyde, the imine or the alkene **155** into the epoxide, aziridine or cyclopropane ring **156** respectively.



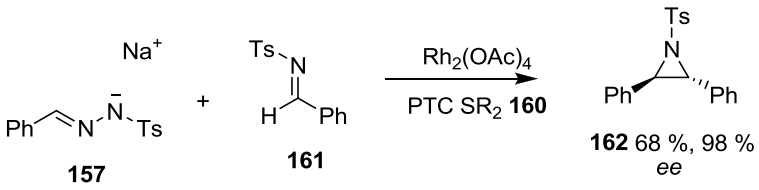
Scheme 76: Aggarwal's mechanism cycles for the synthesis of three membered rings.

On the asymmetric synthesis of epoxides[79], when chiral sulfide **160** was employed the epoxide **159** arose in 82 % yield and 94 % *ee* (Scheme 77).



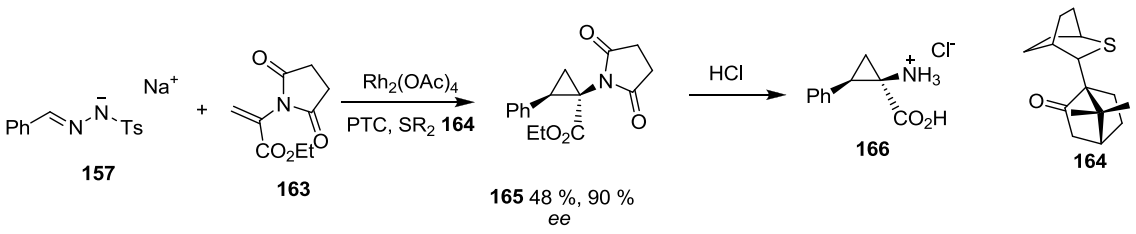
Scheme 77: Asymmetric epoxidation using Aggarwal's method.

When imines were used as electrophiles high yields and *ee*'s were also obtained. The aziridine ring **162** was obtained in 68 % yield and 98 % *ee* when similar conditions were used[80] (Scheme 78).



Scheme 78: Asymmetric aziridination using Aggarwal's method.

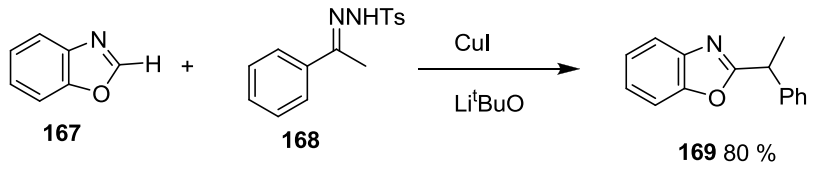
The cyclopropanation of alkenes was explored. The electrondeficient substrate **163** originates **165** in 48 % yield and 90 % *ee*[80] (Scheme 79). After hydrolysis the conformationaly locked α-aminoacid **166** was obtained.



Scheme 79: Asymmetric cyclopropanation using Aggarwal's method.

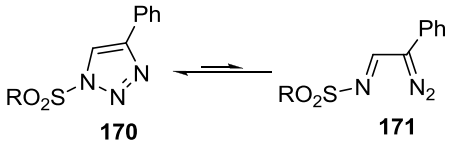
A similar method has been developed by the Wang's group where the base-mediated *in situ* decomposition of tosylhydrazone affords the free diazo compound. Several reactions were developed by employing Copper[81], Rhodium[82] and Palladium[83]

catalysts. The Copper-catalyzed cross-coupling of N-tosylhydrazones with 1,3-azoles[84] afforded products such as **169** (Scheme 80).



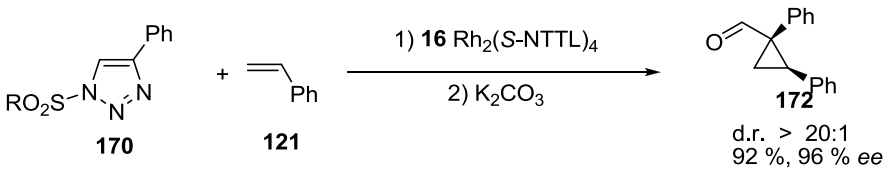
Scheme 80: Copper-catalyzed cross-coupling of N-tosylhydrazones with 1,3-azoles.

The Fokin's group developed a method where the diazo compound is latent under a triazole form[85]. Triazoles can be easily available from the alkyne azide cycloaddition[86]. This process takes advantage of the equilibrium between triazoles **170** and diazo compounds **171**, when electronwithdrawing groups such as the sulfonyl is attached to the N-1 transition metal azavinyl carbenoids can be produced[87] (Scheme 81) though other examples are also available[88]. Once again the potentially explosive diazo compound concentration is maintained low and once formed it reacts with the catalyst.



Scheme 81: The equilibrium between triazoles and diazo compounds.

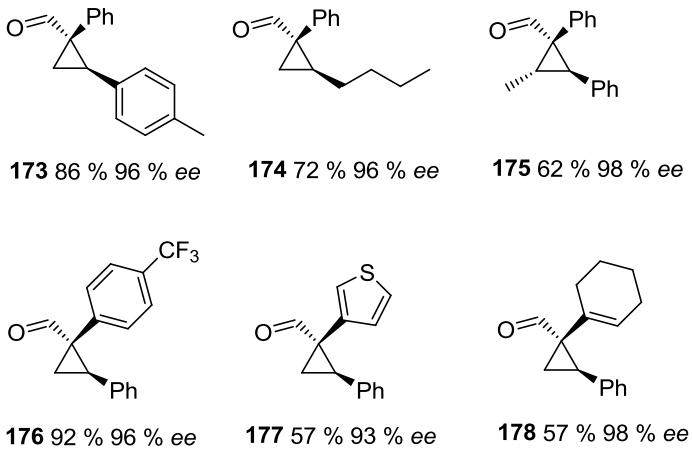
This concept was used to achieve asymmetric cyclopropanations with dirhodium (II) catalysts[89] (Scheme 82). After the cyclopropanation step, the imine is hydrolyzed to the aldehyde:



Scheme 82: Fokin's triazoles on asymmetric cyclopropanation.

Several styrene derivatives were used: with substituents on the aromatic ring, with alkylic a chain, with a disubstituted olefin among others (Scheme 83). Modifications on triazole **170** were also well tolerated, such as with other aromatic substituents and with a

cyclohexene also. Up to excellent yields were achieved and the *ee* were systematically above 90 %.

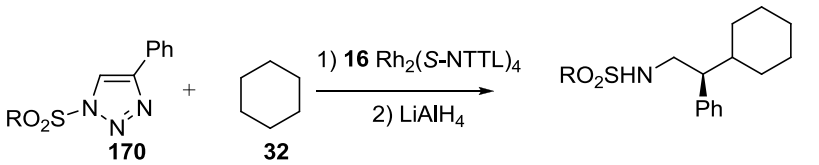


173 86 % 96 % *ee* **174** 72 % 96 % *ee* **175** 62 % 98 % *ee*

176 92 % 96 % *ee* **177** 57 % 93 % *ee* **178** 57 % 98 % *ee*

Scheme 83: Selection of Fokin's triazoles substrate scope on asymmetric cyclopropanation.

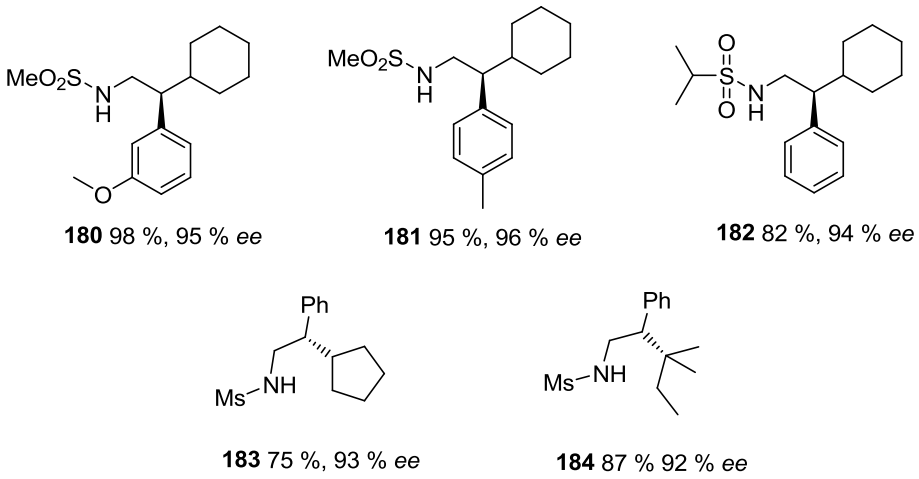
The asymmetric intermolecular C-H insertion is also available[90] for unactivated alkanes such as cyclohexane; after the C-H insertion reaction amine reduction affords product **179** (Scheme 84).



179 95%, 96% ee

Scheme 84: Triazoles on asymmetric C-H insertion.

Substituents on the aromatic ring were well tolerated and the reaction can also functionalize different other alkanes such as cyclopentane and even non cyclic alkanes affording **180**-**184** in yields and *ee* often > 90% (Scheme 85).



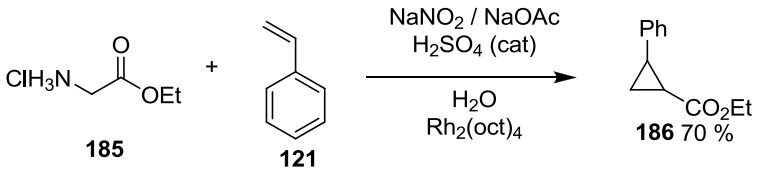
180 98 %, 95 % *ee* **181** 95 %, 96 % *ee* **182** 82 %, 94 % *ee*

183 75 %, 93 % *ee* **184** 87 % 92 % *ee*

Scheme 85: Selection of Fokin's triazoles substrate scope on asymmetric C-H insertion.

Before this reported reaction (2011) only the Rh_2(*S*-DOSP)$_4$ catalyzed methyl phenyldiazoacetate decomposition was known to react with intermolecular C-H bonds to afford similar products, on a matched combination (Scheme 13).

The *in situ* formation of the ethyl diazoacetate was performed in water by Charette *et al.*[91], where the micelles of styrene solubilized the hydrophobic catalyst $Rh_2(oct)_4$ (Scheme 86). **185** was oxidized with sodium nitrite affording the water soluble diazo compound which was rapidly consumed affording **186** in 70% yield.



185 **121** **186** 70 %

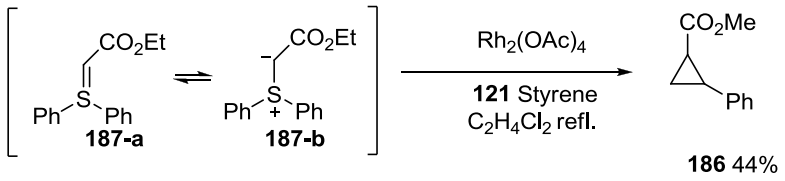
Scheme 86: Cyclopropanation of ethyl diazoacetate formed *in situ* by oxidation.

With these developed methods the diazo is synthesized *in situ* and the dinitrogen liberation still occurs. They don't avoid the diazo compounds but offer some security on substrate handling.

3.1.4. Sulfur Ylides

Sulfonium ylides were already considered as diazo surrogates. The ethyl diazoacetate equivalent **187** is surprisingly stable and remained unchanged for 4 days when dissolved in $CDCl_3$ at room temperature. The diphenyl sulfide byproduct has a high boiling point and therefore its decomposition isn't explosive. Slow addition of

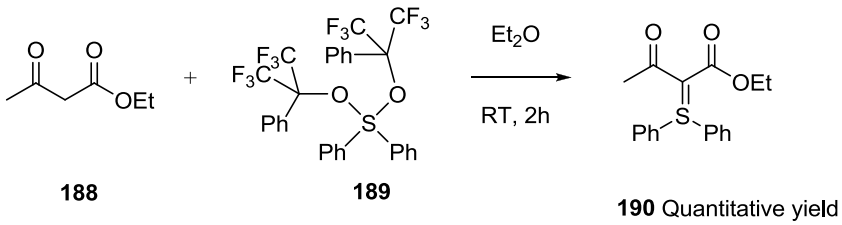
ylide **187** to styrene in the presence of $Rh_2(OAc)_4$ afforded the expected cyclopropane ring in 44 % yield with a diastereomeric ratio of 1:1 (Scheme 87).



Scheme 87: Sulfur ylides on cyclopropanation.

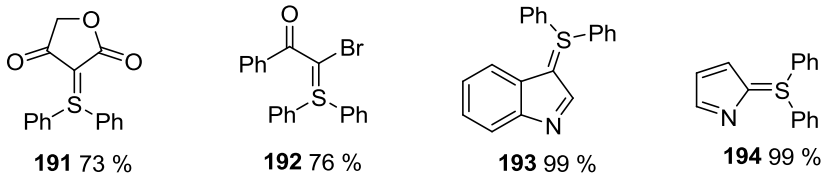
When the reaction was carried with ethyl diazoacetate the ratio modified to 60 % of *trans*. The authors attributed this change to the diphenyl sulfide complexation on the other dirhodium (II) catalyst at axial position. Though when diphenyl sulfide was added to a styrene cyclopropanation with ethyldiazo acetate the ratio didn't changed significantly (58 % of *trans* isomer). Nonetheless, it is enough for the authors to consider a common dirhodium (II) carbenoid specie. Sulfur ylides with two α-substituents are too much stable and can't be easily decomposed.

More recently Maulide *et al.* [92] employed Martin's sulfurane **189** to get disubstitued sulfonium ylides under smooth conditions (Scheme 88).



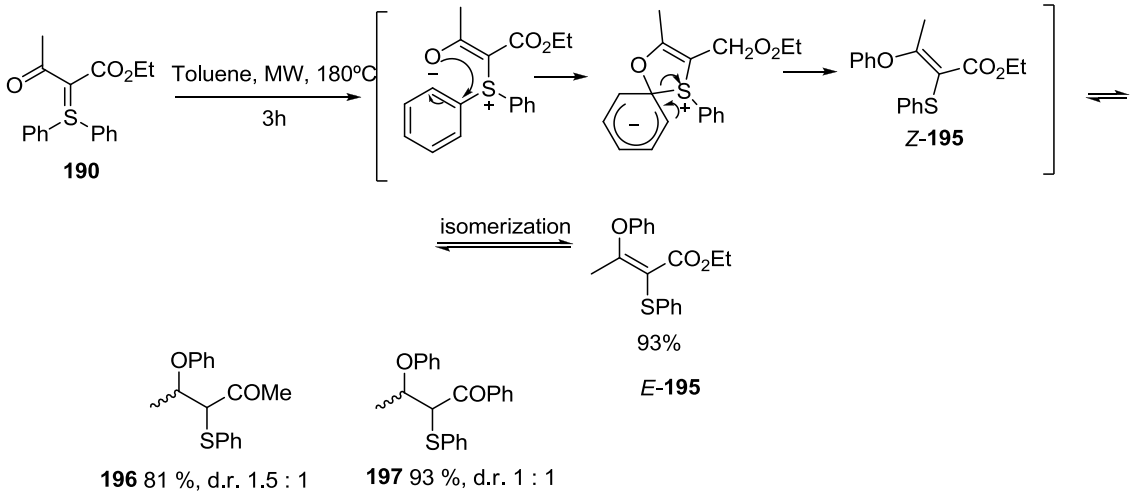
Scheme 88: Maulide's synthesis of sulfur ylides.

The substrate scope was broad and an even heterocyclic compounds such as indoles and pyrroles were employed providing yields up to 99 % (Scheme 89).



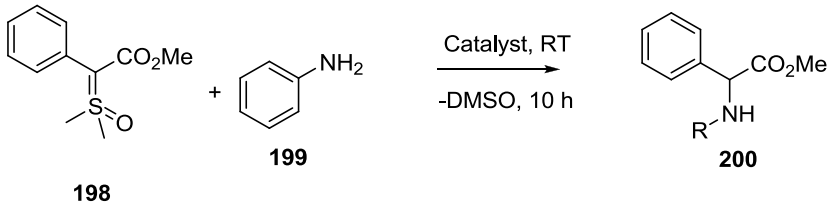
Scheme 89: Selection of the substrate scope of Maulide's synthesis of sulfur ylides.

These sulfonium ylides are also very stable but can react under forcing conditions to obtain tetrasubstituted alkenes. The mechanism probably proceeds with the *ipso*-attack of a negatively charged oxygen atom onto the proximal, activated aromatic ring (Scheme 90).



Scheme 90: Rearrangement of sulfur ylides to tetrasubstitued alkenes.

For many years the Merck researchers showed concern on metal-catalyzed diazo decomposition and on the subsequent reactions, namely the N-H insertion. In 2009 the Merck Department of Process Research published[93] a method for carbenoid X-H insertions with sulfoxonium ylides as carbenoid precursors with the aim of surrounding the diazo functional group. The substrate **198** was synthesized from the decomposition of the respective diazo compound on the presence of DMSO and Cu or Ag[94]. The reaction of **198** with 5 eq. of $Rh_2(OAc)_4$ furnished the product only in 7 % yield and the more electrophilic catalyst $Rh_2(tfa)_4$ in 22 % only with DMSO as byproduct (Scheme 91). These low yields were obtained even with dirhodium (II) catalysts employed in 5 mol% instead of the regular 1 mol % or less were further investigated. A control experiment with added DMSO in 25 mol % was enough to inhibit both catalysts. Once more the sulfur compound byproduct coordinates to the axial positions making them unavailable for the diazo nucleophilic attack. On the other hand, Ru based catalysts afforded the product in 66 % maximum yield and the catalyst $[Ir(COD)Cl]_2$ used on 1 mol % achieved 91 % yield of **200**, being this the catalyst of choice for further applications.

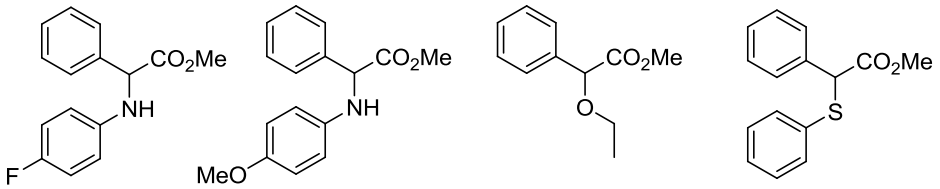


198 199 200

Entry	Catalyst (mol %)	Solvent	200 (%)
1	$Rh_2(OAc)_4$ (5)	Toluene	7
2	$Rh_2(tfa)_4$ (5)	Toluene	22
3	$RuCl_2(Cp)(PPh_3)_2$ (2)	Toluene	66
4	$[Ir(COD)Cl]_2$ (1)	CH_2Cl_2	91

Scheme 91: Selection of Merck's catalyst screening for NH insertion with sulfoxonium ylides.

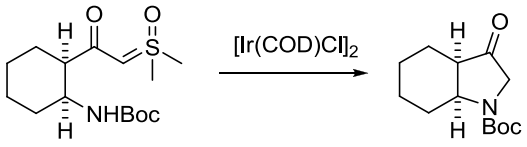
The reaction allows better yields with electronwithdrawing groups on the nucleophilic amine than with electrondonating ones (Scheme 92). Ethanol and thiophenol as nucleophiles also provide very good product yields.



201 93 % **202** 76 % **203** 86 % **204** 80 %

Scheme 92: Selection of Merck's substrate scope catalyzed by $[Ir(COD)Cl]_2$ for carbenoid insertions with sulfoxonium ylides.

The intramolecular N-H insertion was explored where product **206** was obtained in 74% yield (Scheme 93).

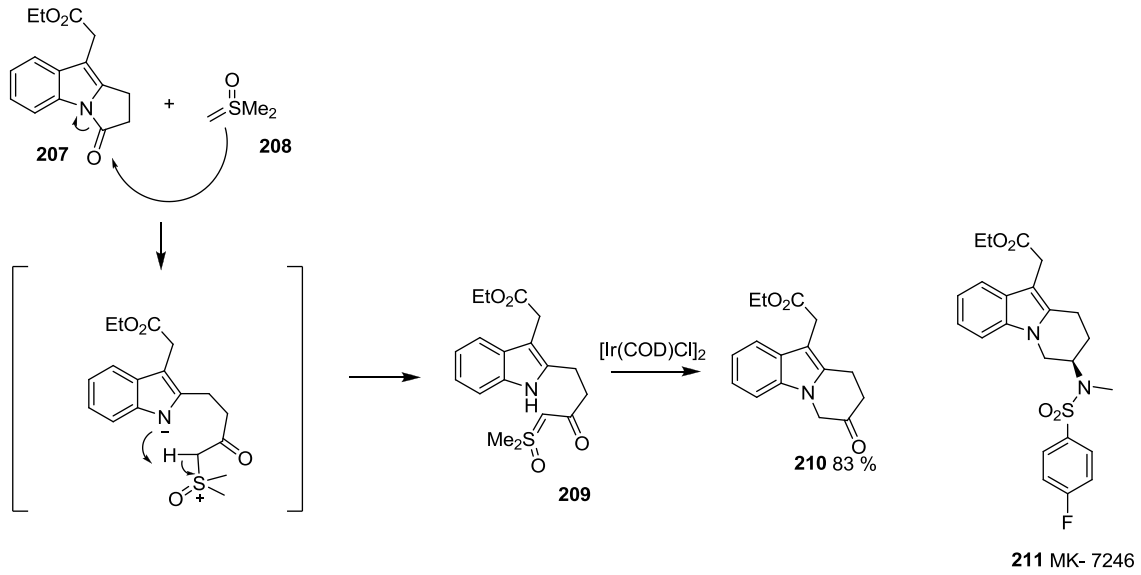


205 **206** 74%

Scheme 93: Intramolecular N-H insertion from carbenoid generated with a sulfoxonium ylide.

In 2012 the Merck's Department of Process Chemistry presented[95] a synthesis for the drug MK-7246 **211**. On this new method the sulfoxonium ylide wasn't synthesized

form the diazo compound but from **208** (derived from Me_3SOI and KO^tBu), then it was decomposed by $[Ir(COD)Cl]_2$ enabling the formation of the product **210** (Scheme 94).

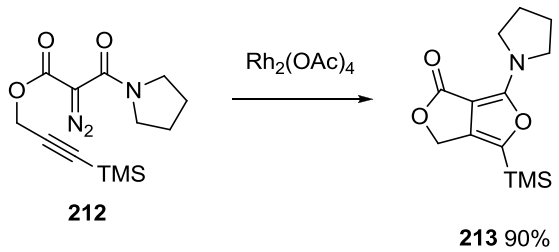


Scheme 94: The N-H insertion on a carbenoid as a synthetic route to MK-7246, by Merck.

This process was later scaled up on a pilot plant (> 100 Kg) to produce enough **211** for the clinical trials. According to the authors, this was the manufacturing route and the most cost effective one form three possibilities, in which the other two didn't made use of the carbenoid N-H insertion.

3.1.5. Cyclopropenes

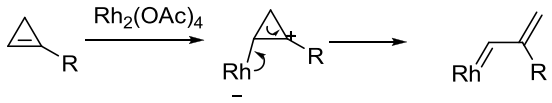
For several years dirhodium (II) carbenoids trapped by alkynes afforded products of much great complexity when the substrate was carefully design[96]. The mechanism for this reaction was unclear but furans as **213** were obtained (Scheme 95):



Scheme 95: Evidence for cyclopropenes ring opening with dirhodium (II) catalysts.

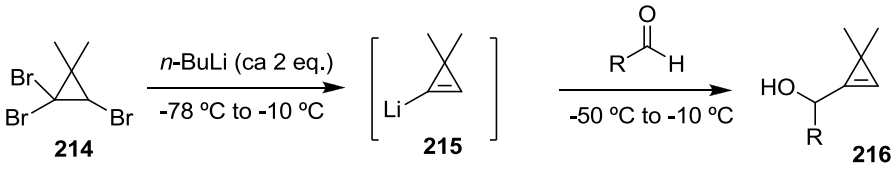
In 2011 Cossy *et al.* disclosed[97] the dirhodium (II) ring-opening of cyclopropenes[98] to form dirhodium (II) vinyl carbenoids. By the cyclopropene's

double bond attack on the rhodium and further Rh π-backdonation the ring collapses (Scheme 96), liberating the high ring strain[99], which renders the metal carbenoid. These carbenoids don't possess the electronwithdrawing group necessary for diazo stabilization.



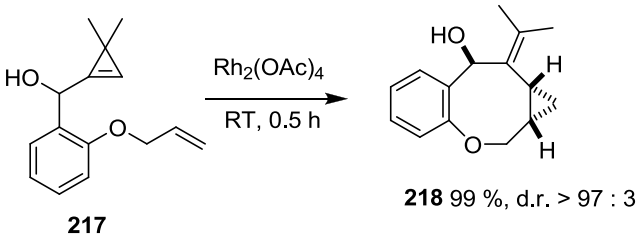
Scheme 96: Generic mechanism of cyclopropenes ring opening with dirhodium (II) catalysts.

Another advantage of this method is the separate synthesis of the cyclopropene which can attack an electrophile (Scheme 97).



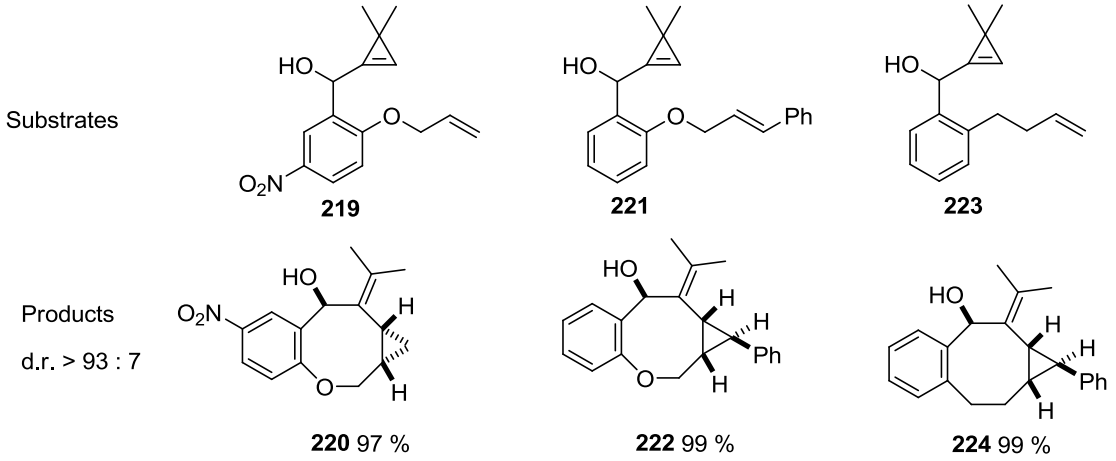
Scheme 97: Synthesis and installation of the cyclopropene ring.

While attempting to cyclize substrate **217** with several gold catalysts, the results were not satisfactory since several unidentified products were obtained with the expected product which could not be completely isolated. Then $Rh_2(OAc)_4$ was considered and afforded the desired product from cyclopropanation in 99 % yield (Scheme 98).



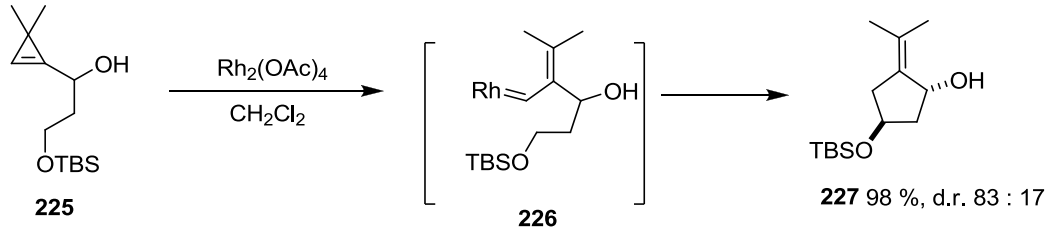
Scheme 98: Rh(II)-catalyzed cyclopropanation from cyclopropenes.

Several substrates designed for cyclopropanation reacted smoothly and the majority within 0.5 h with quantitative yields and excellent diastereomeric ratios (Scheme 99).



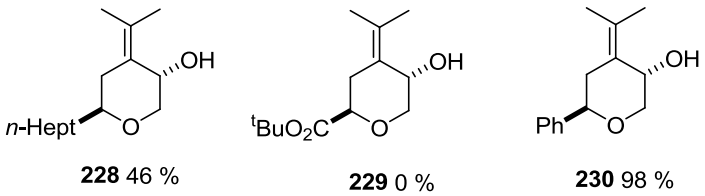
Scheme 99: Selection of Cossy's substrate scope of Rh(II)-catalyzed cyclopropanation from cyclopropenes.

When olefins are not present on the substrate the C-H insertion can be the dominant pathway and the Rh-catalyzed C-H insertion was studied, where product **227** was obtained in quantitative yield[100] (Scheme 100). The nearby oxygen from TBS has a determinant role on the activation of the nearby C-H bond.



Scheme 100: Rh-(II) catalyzed C-H insertion from cyclopropenes.

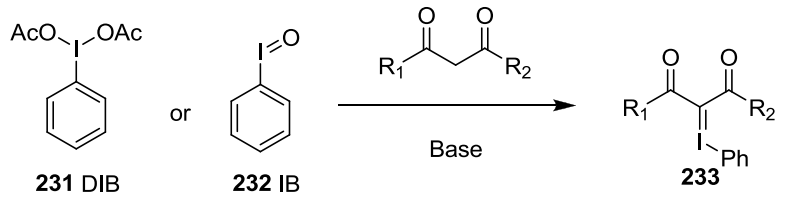
A substrate scope was conducted and the preference for 6-membered ring formation was observed. The poor activation form the *n*-heptyl substituent renders the C-H insertion product **228** in 46 % yield (Scheme 101). Product **229** is not obtained due to the electronwithdrawning group nearby but product **230** with a strongly activated group is obtained is quantitative yield.



Scheme 101: Selection of substrate scope of Cossy's Rh-(II) catalyzed C-H insertion from cyclopropenes.

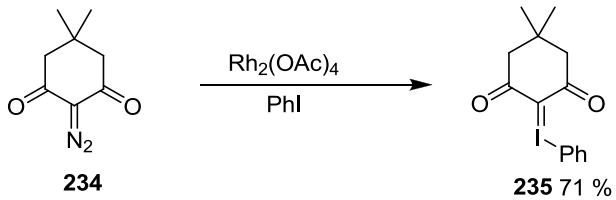
3.1.6. Phenyliodonium Ylides

Phenyliodonium ylides are considered diazo surrogates. They are usually synthesized from diacetoxyiodobenzene **231** (DIB) or from iodosobenzene **232** (IB) (both on +3 oxidation state) with a 1,3-dicarbonyl compound under basic conditions[101] (Scheme 102). Phenyliodonium ylides with just one α-carbonyl substituent are not stable enough to be isolated though they can be synthesized and decomposed *in situ*[102].



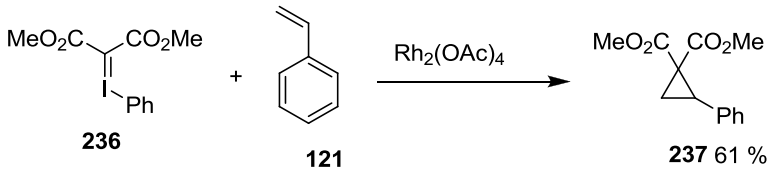
Scheme 102: Most common synthesis of phenyliodonium ylides.

They have also been synthesized from $Rh_2(OAc)_4$–catalyzed diazo decomposition of the cyclic substrate **234** on the presence of iodobenzene[103] (Scheme 103).



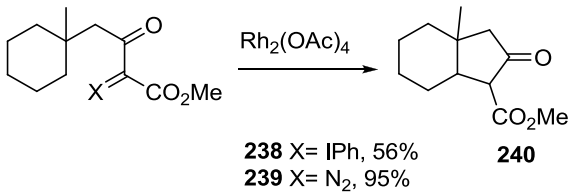
Scheme 103: Synthesis of phenyliodonium ylides from diazo compounds.

Iodonium ylides are regarded as more reactive than their diazo counterparts and when stable they must be stored under low temperatures. They are not explosive since their decomposition affords iodobenzene which is liquid at RT. The precursors DIB and IB are shelf-stable, unlike azides used as diazo transfer reagent. Nevertheless, phenyliodonium ylides are very difficult to purify once they decompose during column chromatography. Their oxidizing properties also decompose the regular Rh(II) catalysts and higher loadings are often required[102c]. Nonetheless phenyliodonium ylides have been used successfully on olefin cyclopropanation (Scheme 104).



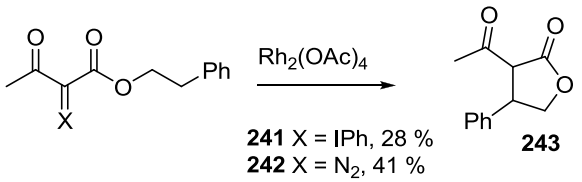
Scheme 104: Cyclopropanation with phenyliodonium ylides.

The metal-catalyzed intramolecular C-H insertion of iodonium ylides is reported. Whereas $Rh_2(OAc)_4$ achieved almost quantitative yield on C-H insertion from the diazo substrate **239**, the iodonium ylide provided **240** in only 56 % (Scheme 105)[104].



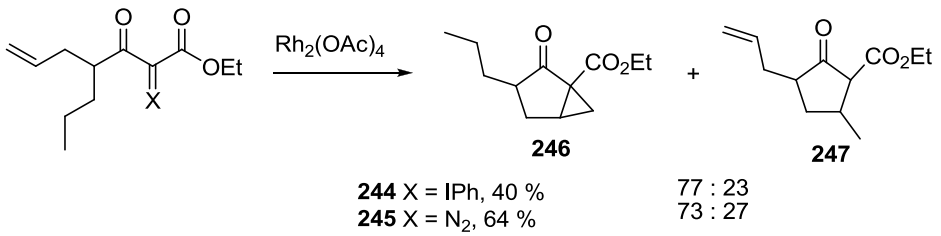
Scheme 105: Comparison of Rh(II)-catalyzed C-H insertion with diazo and iodonium ylide compounds.

The C-H insertion to form heterocycles also affords depleted yields when using the phenyliodonium ylide[104] (Scheme 106).



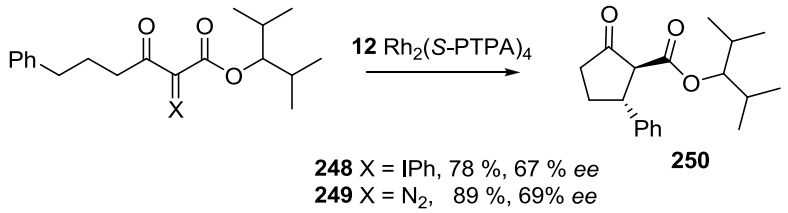
Scheme 106: Comparison of Rh(II)-catalyzed C-H insertion with diazo and iodonium ylide compounds to form a γ-lactone.

A competitive Rh(II)-catalyzed experiment between C-H insertion *vs* cyclopropanation afforded similar selectivities with both diazo and iodonium ylide, which supported a common carbenoid intermediate, though the combined yield from the diazo compound is significantly higher[104] (Scheme 107).



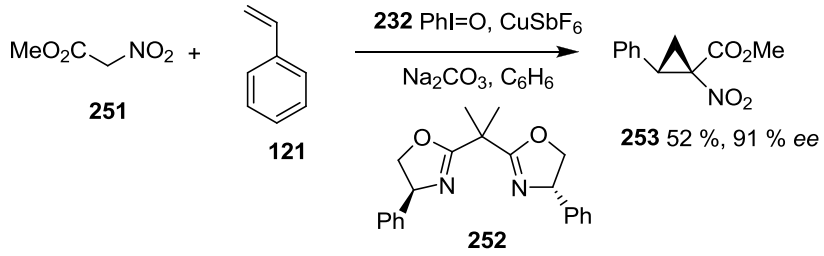
Scheme 107: Competitive experiment of cyclopropanation *vs* C-H insertion.

An asymmetric C-H insertion with C-C bond formation[102b, 104], catalyzed by Hashimoto's Rh_2(*S*-PTPA)$_4$ **12** afforded similar *ee* with both diazo and phenyliodonium ylides, once more the yield was inferior with the iodonium ylide.



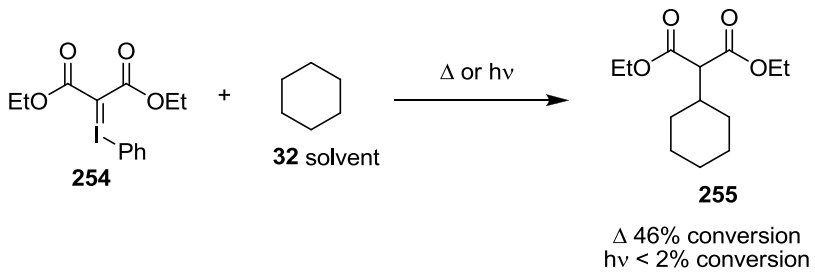
Scheme 108: Comparison between Rh_2(*S*-PTPA)$_4$-catalyzed asymmetric C-H insertion from iodonium ylide and diazo compound.

Charette *et al.*[105] performed the *in situ* generation of the phenyliodonium ylide of methyl nitroacetate **251**, since this wasn't stable enough to be isolated, under the presence of a Cu catalyst and styrene, affording methyl nitroacetate cyclopropanes (Scheme 109).



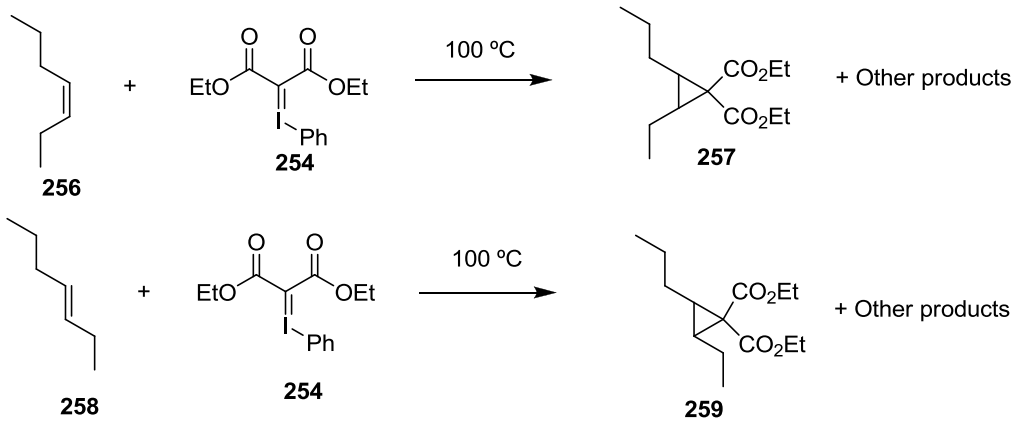
Scheme 109: Asymmetric cyclopropanation *via* an *in situ* generated phenyiodonium ylide.

Another evidence of carbenoid intermediacy was performed by the metal-free C-H insertion of an isolated iodonium ylide **254** which was performed under thermal and photochemical conditions[106]. The thermal reaction under 100 ºC in a sealed tube afforded the C-H insertion product **255** with cyclohexene in 46 % conversion (^{1}H NMR). By the photochemical reaction at RT, < 2% of **255** was obtained. The authors justify this low yield with the poor solubility of substrate **254** in cyclohexane at RT.



Scheme 110: Metal-free C-H insertion of a phenyliodonium ylide.

The spin state of the intermediary was also analyzed. Cyclopropanation of **254** with *cis*-3-heptene at 100 ºC afforded **257** and < 2% of **259**; and with *trans*-3-heptene it afforded also mainly **259** with < 1% of **257**. According to the authors, the high degree of stereospecificity retention indicates cyclopropanation of the double bond *via* a singlet carbene.

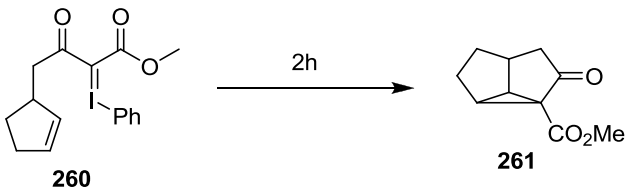


Scheme 111: Mechanistic study to determine the nature of the intermediate.

The photolysis of **254** with *cis*-3-heptene produced low yields of cyclopropanation products, but instead a mixture of **257** product and **259** product was obtained in a ratio of 34 : 66. The *trans*-3-heptene afforded **257** and **259** in ratio of 22 : 78. The loss off stereospecificity was attributed to intersystem crossing of photoexcited **254** that likely undergoes intersystem crossing and leads to triplet carbene.

In 2010 Moriarty *et al.* published a metal-free intramolecular alkene cyclopropanation from iodonium ylides[107]. On the reaction optimization, **260** was cyclized to **261** under various conditions. With CuCl the three-membered ring product was obtained in 95 %, with $Rh_2(OAc)_4$ a low yield was obtained (~20 %) while the thermal decomposition in refluxing CH_2Cl_2 afforded **261** in 75% and by UV radiation

originated 58 - 60 % yield. Since the second best yield didn't involved metal-catalyst (entry 7) the thermal decomposition was selected by the authors for substrate scope.

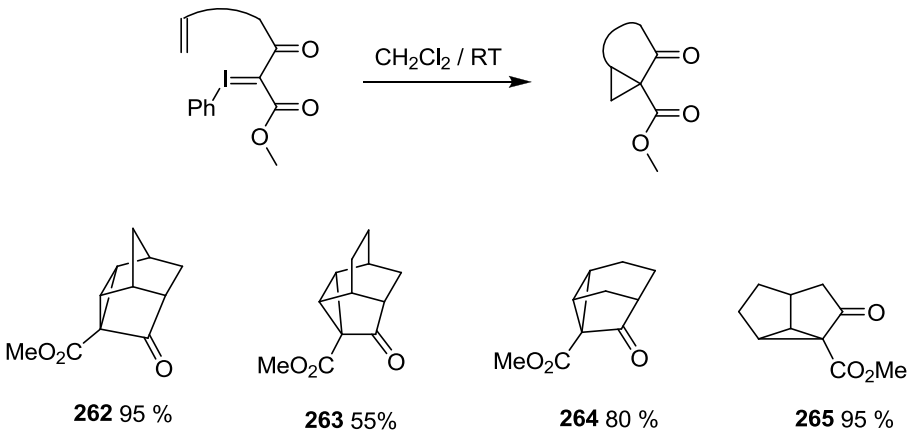


260 **261**

Entry	Promoter	Conditions	261 (%)
1	CuCl	CH_2Cl_2, 0 ºC to RT	95
2	$CuCl_2$	CH_2Cl_2, 0 ºC to RT	58-65
3	$Cu(acac)_2$	CH_2Cl_2, 0 ºC to RT	58-60
4	$Rh_2(OAc)_4$	CH_2Cl_2, 0 ºC to RT	~ 20 (complex mixture)
5	$Rh_2(OAc)_4$	CH_2Cl_2, -40 ºC to RT	~ 50 (complex mixture)
6	Thermal	CH_2Cl_2, reflux	~ 10 - 12
7	Thermal	CH_2Cl_2, reflux (12 h)	75
8	UV	$CDCl_3$ (3h)	58 - 60
9	Pd $(OAc)_2$	CH_2Cl_2, 0 ºC to RT	(complex mixture)

Scheme 112: Selected promoters of metal-free intramolecular alkene cyclopropanation.

The substrate scope was applied to substrates in which the high stain release from the cyclic double bond aids the product formation (Scheme 113).

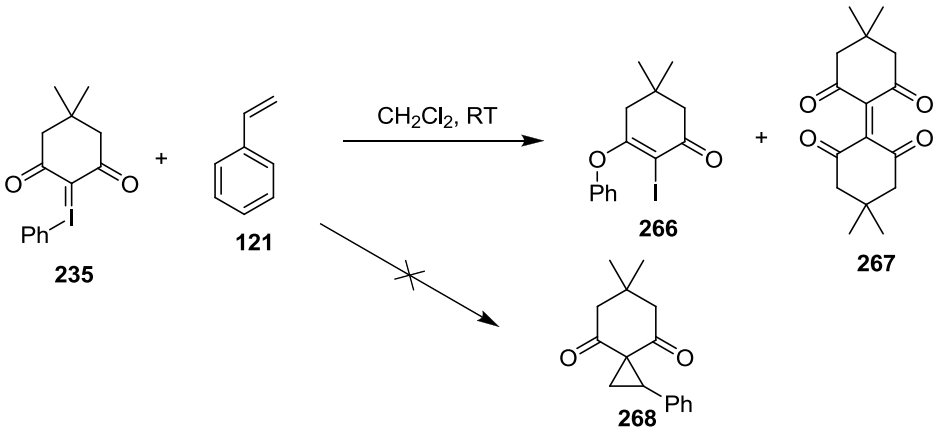


262 95 % **263** 55% **264** 80 % **265** 95 %

Scheme 113: Selection of Moriarty's substrate scope of metal-free intramolecular alkene cyclopropanation from iodonium ylides.

The authors tried to perform an intermolecular cyclopropanation, with several other alkenes and under the same smooth and metal-free conditions, but only products from 1,4-phenyl migration **266** and the dimerization of ylide **235** were obtained. However,

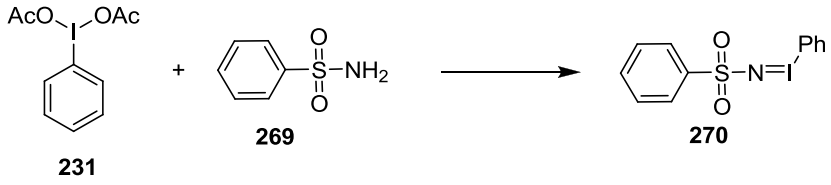
when the reaction was carried out in the presence of $Rh_2(OAc)_4$ the cyclopropanation product **268** was obtained in very good yields and therefore, according to the authors, a carbene pathway is ruled out.



Scheme 114: Attempt to carry an intermolecular metal-free cyclopropanation with phenyliodonium ylides at RT.

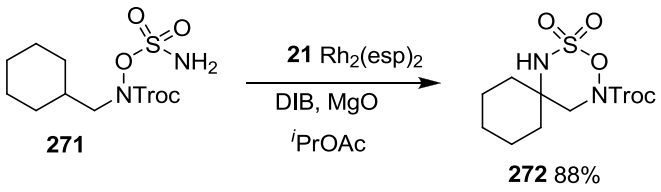
The phenyliodonium ylides as diazo surrogates haven't been very explored, since their dependence of 1,3-dicarbonyl compounds, difficult purification and general lower yields, makes them less appealing for C-H insertion reaction with C-C bond formation.

In opposition, far more developed is the C-H insertion with N-C bond formation where sulfonamide-derived aryliodinanes **270** is formed *in situ* with DIB[108] (Scheme 115).



Scheme 115: Formation of sulfonamide-derived aryliodinanes.

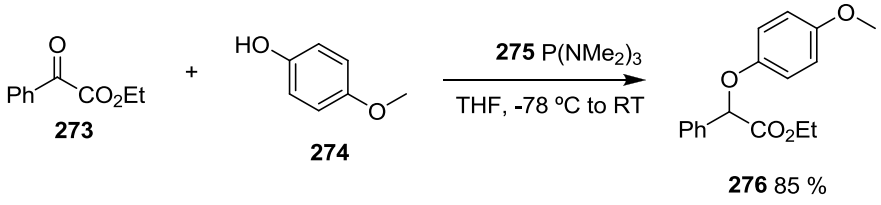
This nitrene insertion has a preference for 6-membered ring formation and alkane C-H bonds can be specifically activated[109] (Scheme 116). The $Rh_2(esp)_2$ **21** enhanced stability being the catalyst of choice for these reactions and the base MgO is added to scavenge the acetic acid. Before the use of DIB the decomposition of azides with dinitrogen liberation was regularly employed[108].



Scheme 116: $Rh_2(esp)_2$-catalyzed nitrene insertion on a C-H bond.

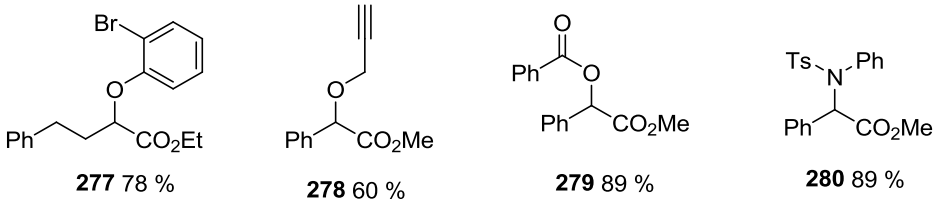
3.1.7. α-Keto Esters

α-keto esters were used as diazo surrogates, *via* a nonmetal approach, in presence of tris(dimethylamino)-phosphine **275**[110]. The X-H insertion (X= O, N) was performed and compound **276** was obtained in 85 % yield (Scheme 117).



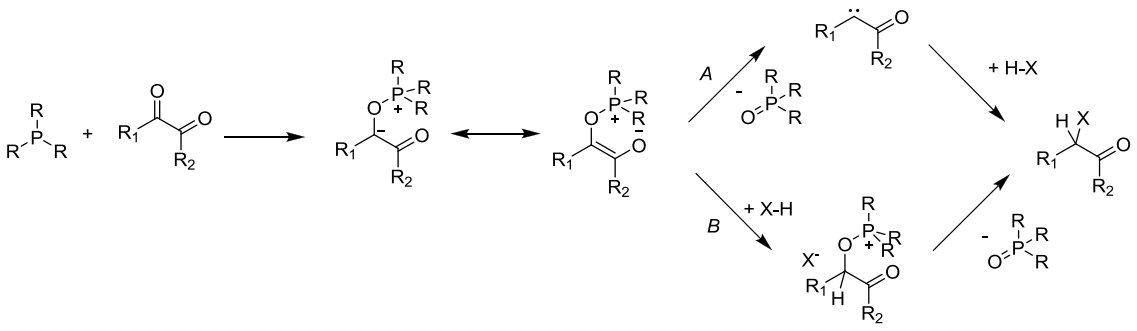
Scheme 117: α-keto esters as diazo surrogates.

The reaction afforded the construction of diversified scaffolds (Scheme 118).



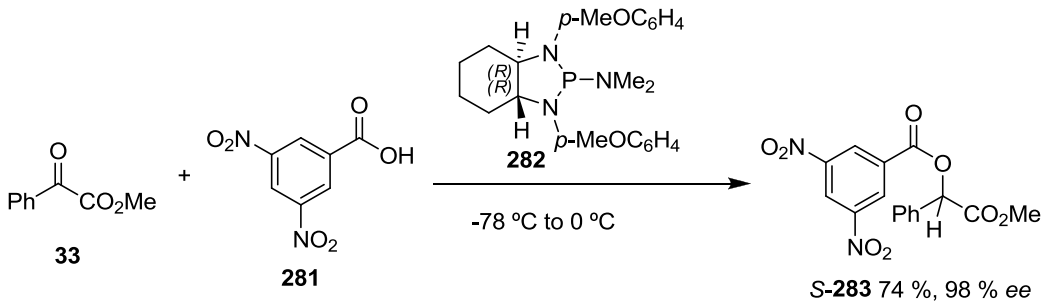
Scheme 118: Selection of α-keto esters as diazo surrogates substrate scope.

Mechanistically, the authors believed that the reductive X-H functionalization is initiated by condensation of the phosphine to the α-keto ester substrate (Scheme 119). Then, the dipolar intermediate could follow two distinct mechanistic pathways. The loss of the phosphine oxide could render the free carbene in solution (path *A*), which would be captured by the X-H and then lead to the product. Alternatively, the dipolar intermediate could be intercepted by proton transfer from the nucleophile X-H (path *B*). Further displacement of the alkoxyphosphonium intermediate by a nucleophile world furnish the product.



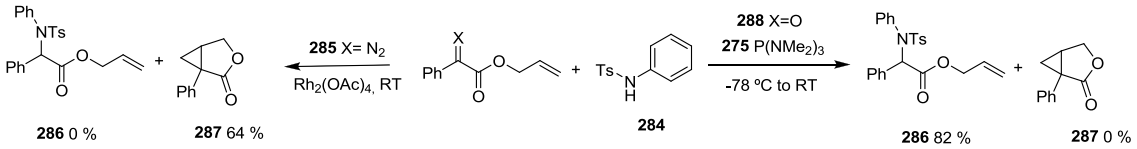
Scheme 119: Reported possible mechanisms for X-H functionalization from α-keto esters.

The mechanistic pathways were differentiated by the use of a chiral phosphine **282** (Scheme 120). In an event of a stepwise polar mechanism (path *B*) the stereospecific protonation of the intermediate followed by stereospecific displacement of the phosphoric triamide leaving group would yield the asymmetric product **283**. By contrast if a free carbene was generated, the product would be racemic (path *A*). The product *S*-**283** was obtained with 98 % *ee* which points to a stepwise polar mechanism (path *B*).



Scheme 120: Asymmetric induction on the O-H functionalization from α-keto esters with a chiral phosphine.

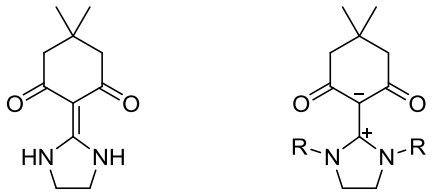
Another evidence of a non carbene pathway is presented on Scheme 121. A competitive reaction using substrate **288** with tris(dimethylamino)-phosphine **275** afforded only the N-H insertion product **286** in 82 % yield, while the diazo parent afforded exclusively the cyclopropanation product **287** on a Rh (II)-catalyzed reaction.



Scheme 121: Competitive experiment N-H functionalization *vs* cyclopropanation on α-keto esters.

3.1.8. N-Heterocyclic Carbenes

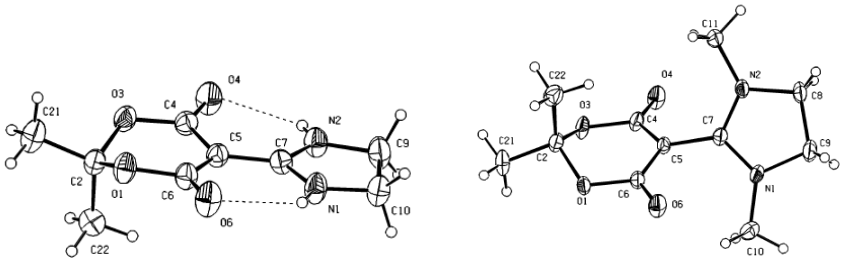
The NHC's with strong electrondonation capabilities made them case studies on olefin polarization[111]. In such compounds the NHC acts as a donor group on one olefin side while the other has electronactractor groups. They are very polarized and can be seen as a zwitterionic bond instead of a regular double bond, especially when R substituents are bulky[112] (Scheme 122).



288 **289**

Scheme 122: Zwitterionic character of alkenes with NHC's and bulky R groups.

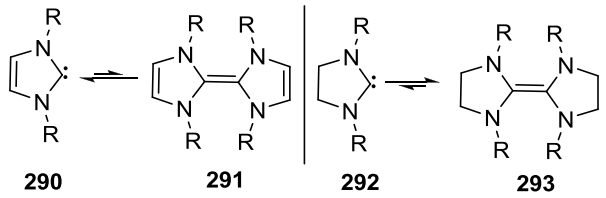
These effects can create an angle that can be > 45º between the NHC and the electronattractor part, disrupting the π system. On **288** there is a hydrogen bond between the N-H and the carbonyl group and the molecule is planar, but on **289** (R=Me) the substitution of the hydrogens by methyl groups creates an angle of 53º around the double bond, as can be observed by the single crystal X-ray image on Scheme 123.



288 **289** (R= Me)

Scheme 123: Single crystal X-ray images of the planar (left) and twisted double bond (right).

On free NHC's, despite the structural difference between **290** and **292** it's only a double bond, **292** is prone to dimerize with small R substituents while **290** is stable as a monomer[44, 113] (Scheme 124).



Scheme 124: The relative stability of the N-heterocyclic carbene.

Such compounds were not yet evaluated as diazo surrogates, but the equilibrium of **292** towards dimerization can remove it from taking part on side reactions.

3.2. Results and Discussion

The main objective of this Ph. D. study was to develop a viable methodology which enables the replacement of diazo functional group for carbene generation, in order to perform C-H insertions with C-C bonds formation, as a non toxic and non explosive alternative.

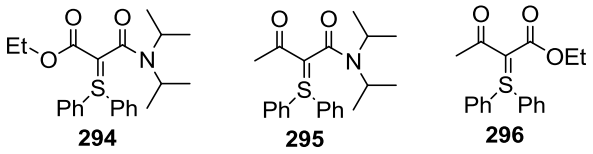
As described before, diazo compounds are widely employed on metal carbenoid formation with dinitrogen extrusion. They form catalytically highly reactive transient carbenoid species with metals as Rhodium, Copper or Ruthenium, among others. These are usually employed on cyclopropanation / cyclopropenation, ylide generation or C-H insertion on inactivated sp^3 carbons. Cu-based catalysts are more used to cyclopropanation and ylide transfer reactions while Rhodium(II) dimmers like $Rh_2(OAc)_4$ are known to catalyze the C-H insertion reaction, where other metal catalysts often are not so selective. The dirhodium (II) catalysts family has emerged as a matched pair for this reaction and several chiral catalysts are available[15]. They can achieve excellent enantioinduction levels with high yield and low catalyst loadings are commonly employed, such as 1 mol %. Both intramolecular and intermolecular C-H insertions with C-C bond formation are available with broad substrate modification tolerance. These reactions are known for the activation of C-H bonds which can´t be seen as functional groups otherwise and heterocycles can be easy synthesized by this method.

Despite being a field very explored on the small laboratory scale, on industrial scale these advances have found little applicability and only very few processes use the C-H insertion / C-C bond formation technology, despite it offers new disconnection approaches with the possibilities of shorten synthesis with better yield and lower waste amounts. Rhodium is a precious metal and its high cost is a drawback which can be circumvented by catalyst reuse, but the diazo associated risks can't be so easily surrounded. The rapid dinitrogen liberation can trigger an explosion and they are toxic and carcinogenic also. Besides diazo compounds are usually synthesized from azide reagents, another potentially explosive reagent. The diazo moiety *in situ* formation and decomposition offers some protection though it doesn't completely solve the problem; sulfur ylides, as diazo functional group surrogate, lack reactivity or the sulfur byproduct can deactivate the dirhodium (II) axial positions. On the other hand, phenyliodonium

ylides are difficult to purify, they usually require 1,3-dicarbonyl compounds to a successful ylide formation and their oxidizing properties can decompose the catalyst. Finally cyclopropenes are a suitable alternative, though they can only afford vinyl metal carbenoids and the electronwithdrawing α-substituent is usually considered necessary to its desired reactivity. Since the reported approaches don't offer a convenient solution for the C-H insertion with C-C bond formation reaction, the work here described was developed in order to face such problem.

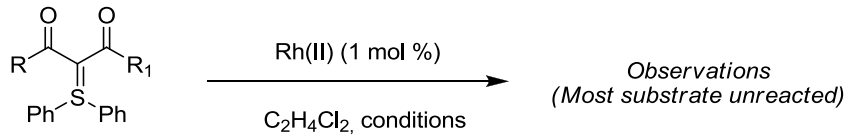
3.2.1. Metal Carbenoid Formation Without Diazo Compounds

Initially the sulfonium ylides **294-296** were evaluated for metal carbenoid formation and were synthesized with collaboration with the laboratory of Prof. Dr. Nuno Maulide. **294** and **295** were intended for intramolecular C-H insertion while **296** for styrene cyclopropanation (Scheme 125).



Scheme 125: Sulfur ylides evaluated on metal carbenoid formation.

These sulfur ylide substrates were initially evaluated with dirhodium (II) catalysts (Scheme 126).



Entry	Substrate	Catalyst	Conditions	Observations[a]
1	**294**	$Rh_2(OAc)_4$ **5**	3h RT→17h 60ºC→ 24h reflux	> 80% remaining substrate
2	**295**	$Rh_2(OAc)_4$ **5**	2h RT→ 19h reflux	>76% remaining substrate
3	**296**	$Rh_2(OAc)_4$ **5**	4Å MS, styrene (4 eq.) 3h RT → 68h 40ºC	>99 % remaining substrate
4	**295**	$Rh_2(tfa)_4$ **86**	6h RT→17h 60ºC → 24h reflux	>75% remaining substrate
5	**295**	$Rh_2(cap)_4$ **12**	5h RT→17h 60ºC→ 24h reflux	51% remaining substrate Complex mixture.

[a] conversions determined by ^{1}H NMR.

Scheme 126: Decomposition attempts of sulfur ylides with dirhodium (II) catalysts.

The $Rh_2(OAc)_4$ reactions with sulfur ylides **294-296** were carried out. The reactions were induced firstly at RT at then since no decomposition was observed by TLC the temperature was raised. Nonetheless most substrate remained unreacted and other Rh(II) catalysts were employed. $Rh_2(tfa)_4$ and $Rh_2(cap)_4$, catalysts with more elctronwithdrawing and electrondonating ligands respectively, were used with **295**, a high percentage of **295** was still unreacted and no desirable product formation was observed. Then, other known diazo catalyst promoters for cyclopropanation were tested (Scheme 127).

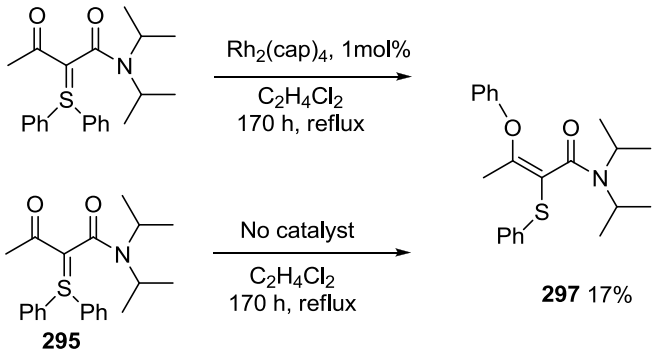
296

Entry	Catalyst (eq.)	Conditions	Observations[a]
1	$Cu(OAc)_2 \cdot H_2O$ (10mol%)	23h, 60ºC	>99 % remaining substrate
2	1) $Cu(CF_3SO_3)_2$ 2) CuI (10mol%)	1) 22h, 60ºC 2) 27h, 60ºC	>90 % remaining substrate
3	ZnEtI (2.5 mol%)	3h RT→23h, 60ºC	>68 % remaining substrate (no product)
4	ZnI_2 (10 mol%)	24h, 60ºC	>99 % did not reacted

[a] conversions determined by ^{1}H NMR.

Scheme 127: Decomposition attempts of sulfur ylide **296** with Cu and Zn catalysts.

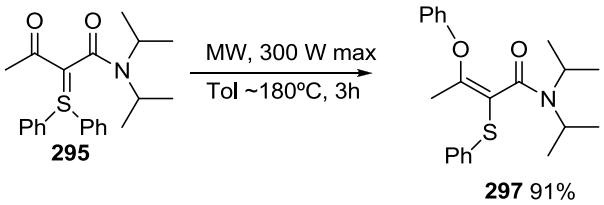
The reaction with Cu- and Zn[114]-based catalysts didn't afforded the desired cyclopropane product. Since no product was obtained and the reaction with $Rh_2(cap)_4$ in refluxing $C_2H_4Cl_2$ for 170 h gave a similar crude NMR spectra with a control without catalyst, they were purified together (Scheme 128).



Scheme 128: Isolation of product **297**.

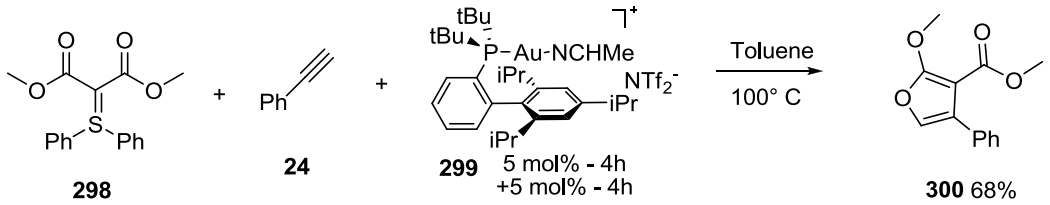
Compound **297** was isolated in 17 % yield as the only compound isolated. This product is the tetrasubstituted alkene[92] that arises from the mechanism presented on Scheme 90.

Then, the rearrangement under microwave irradiation (MW) was tested (Scheme 129). As expected, the tetrasubstituted alkene **297** was again obtained in a clean reaction.



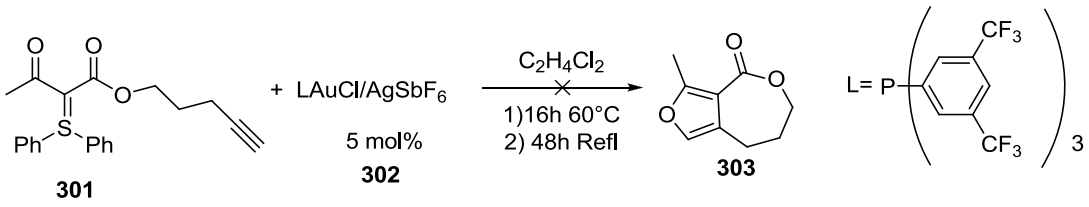
Scheme 129: Rearrangement of **295** by MW.

During my stay at the Max-Planck-Institut für Kohlenforschung (Germany) on Prof. Dr. Nuno Maulide's laboratory the work was developed with collaboration with Prof. Dr. Xueliang Huang, Dr. Marco Luparia and Dr. Bo Peng. On the ongoing sulfur ylide decomposition project with gold(I) catalysts, the Echavarren's catalyst **299** was used to decompose **298** and with **24** it affords the furan ring **300** (Scheme 130).



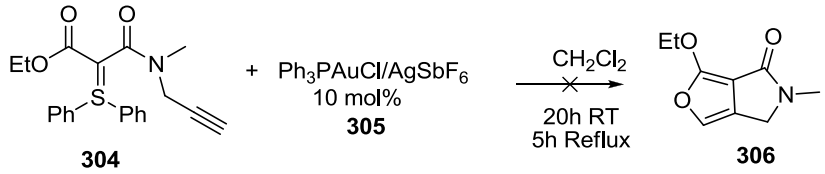
Scheme 130: Gold(I)-catalyzed furan formation from sulfur ylide with acetylene.

Two catalyst loadings were used for this intermolecular reaction. Despite the respective reaction with Rh(II)-catalyzed diazo decomposition affords the same products via a metal carbenoid reaction, here the DTF calculations showed that this reaction does not proceed *via* metal-carbenoid but with a different mechanism[115]. This explains the lack of reactivity towards substrate **301**, even when a more electrophilic Au (I) catalyst was used (Scheme 131). The reaction with a shorter alkane chain, by one C, near the alkyne succeeds, affording the product in very good yield.



Scheme 131: Attempt on cyclization of substrate **301** with a gold (I) catalyst.

The reaction of **304** with the gold catalyst **305** also didn't afforded the product, but when the ester moiety is replaced by an acetyl the product is obtained (Scheme 132).

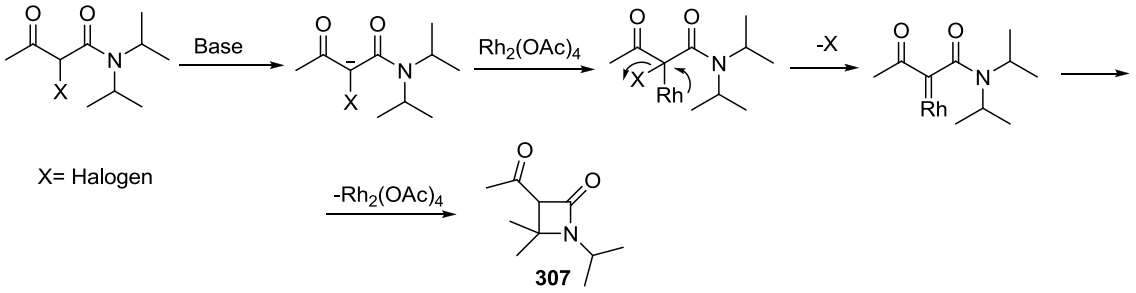


Scheme 132: Attempt on cyclization of substrate **304** with a gold (I) catalyst.

As described on the literature sulfonium ylides are very stable[102c] and only the most reactive ones can engage on metal-catalyzed reactions. Since no metal carbenoid was obtained, the sulfonium ylides were discarded and another research line was followed.

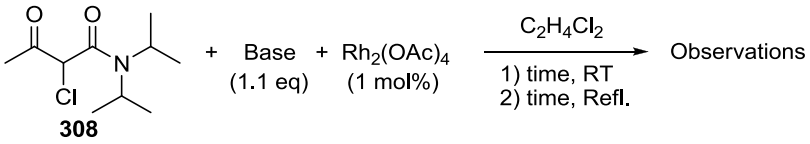
In another approach, the good leaving group properties of halogens were explored towards the metal carbenoid formation (Scheme 133). It was explored the base-induced

metal carbenoid formation by displacement of a halogen α to the carbonyls with the following proposed mechanism: the base would abstract the α-proton leaving a negative charge which is stabilized by two carbonyls; then it would attack the axial position of the dirhodium (II) and the π backbonding would remove the halogen. Then, the complexed carbenoid could react on the usual manner, where the C-H insertion / C-C bond formation would form the β-lactam product **307** (Scheme 133).



Scheme 133: Generic mechanism of a possible base-induced metal carbenoid formation by displacement of a halogen α to the carbonyl groups.

The substrates containing the α-bromo and α-cloro were synthesized and the analog with the α-iodo isn't stable enough and decomposes after a couple of hours and therefore can't be purified and used. Several organic and inorganic bases were used. Firstly the reaction was carried at RT and then for the cases in which the TLC didn't reveled significative conversion they were refluxed. Then, the reaction mixtures were analyzed by ^{1}H NMR to check for product formation. The results with substrate **308** are presented in Scheme 134.



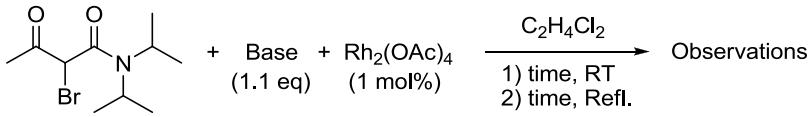
Entry	Base	RT, t (h)	Reflux, t (h)	Observations[a]
1	*N*,*N*-Diisopropylethylamine (DIPEA)	3.5	2.5	NC
2	1,8-Diazabicycloundec-7-ene (DBU)	3.5	2.5	CM, SR
3	1,4-Diazabicyclo[2.2.2]octane (DABCO)	3.5	2.5	NC
4	Triethylamine (Et_3N)	3.5	2.5	NC
5	2,6-Lutidine	3.5	2.5	NC
6	1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	3	2.5	NC
7[b]	*p*-Toluenesulfonic acid (*p*-TSA)	3	2.5	NC
8	K_2CO_3	3	2.5	NC
9	$Ca(OH)_2$	3	2.5	NC
10	$Li_2(CO)_3$	3	2.5	NC

[a] CM = complex mixture; SR= significative amount of substrate remaining; NC= no conversion [b]an acid was used

Scheme 134: Bases screening for the attempts of metal carbenoid formation via substrate **308**.

Several N-based bases were used (Scheme 134, entries 1- 6) but only with DBU the substrate was consumed, without the desired C-H insertion product formation, **307**. A blank without catalyst was performed. Both ^1H NMR spectra of the reaction mixtures were similar, so the catalyst isn't necessary for the reaction to proceed. The inorganic bases didn't afforded any substrate consumption as well.

In line with the previous unsucessful attempts, substrate **309** was tested under the same conditions.



309

Entry	Base	RT, t (h)	Reflux, t (h)	Observations[a]
1	*N*,*N*-Diisopropylethylamine (DIPEA)	3.5	2.5	CM , SR
2	1,8-Diazabicycloundec-7-ene (DBU)	6	-	CM
3	1,4-Diazabicyclo[2.2.2]octane (DABCO)	3.5	2.5	CM , SR
4	Triethylamine (Et_3N)	3.5	2.5	NC
5	1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	3	2.5	CM
6	2,6-Lutidine	3	2.5	NC
7[b]	*p*-Toluenesulfonic acid (*p*-TSA)	3	2.5	NC
8	Quinine	3.5	2.5	CM, SR
9	K_2CO_3	3	2.5	NC
10	$Ca(OH)_2$	3	2.5	NC
11	Li_2CO_3	3	2.5	NC

[a] CM = complex mixture; SR= significative amount of substrate remaining; NC= no conversion [b]an acid was used

Scheme 135: Bases screening for metal carbenoid formation via **309**.

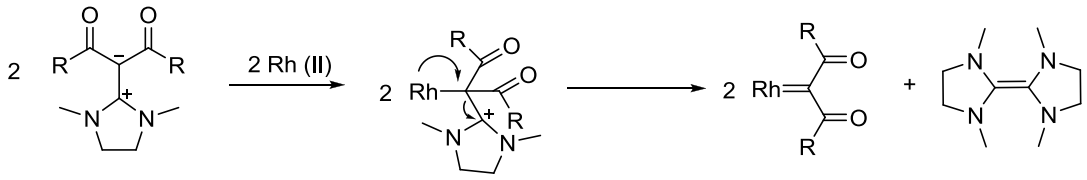
Substrate **309** was more reactive than **308** and several N-based bases afforded some substrate consumption, but without product **307** formation. The reaction with DBU was carried on at RT and was observed that **308** can be decomposed under these mild conditions. Again, a blank experiment was performed without catalyst and in the presence of DBU, providing the same ^{1}H NMR spectra as in the presence of Rh(II) catalyst. In addition, by performing the reaction in higher scale (30 mg *vs* 100 mg) only very small amounts of unidentified products were obtained after purification.

One explanation for those results may derive of nitrogen based-bases that can coordinate to the catalyst's axial positions, blocking them but the inorganic bases don't and they didn't afford any substrate consumption.

Since no product **307** was ever observed this method was abandoned.

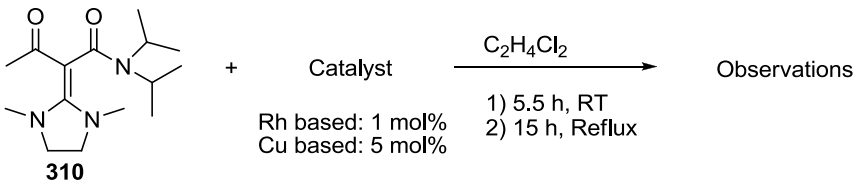
Next, the N-heterocyclic carbene was evaluated as possible diazo surrogate. Taking advantage of the dimerization equilibrium of the monomer NHC (Scheme 124), the free NHC with a saturated backbone would be removed from predictable side reactions such as coordination on dirhodium (II) axial position, deactivating the catalyst. The reaction mechanism presented on Scheme 136 was devised. Since the NHC with N-substituents has a significant torsion angle, a zwitterionic character between the NHC unit and the

substrate is predictable, much like the diazo moiety. This negative charge would attack the dirhodium (II) catalyst at the electrophilic axial position, then the π-backdonation would form the metal carbenoid double bond with NHC extrusion. The depicted NHC isn't stable as monomer and it may dimerize, removing it from side reactions. If it coordinates the dirhodium (II) at axial position the other axial position remains free, as observed by Snyder, Arduengo III *et al.*[47] (Scheme 33) and another substrate can coordinate which displaces this NHC. The dirhodium (II) carbenoid would then follow its typical reactivity.



Scheme 136: A plausible mechanism for Rh(II)-carbenoid formation.

Substrate **310** was synthesized and its reactivity studied with several catalysts. Rh-based catalysts were used in 1 mol % and copper ones in 5 mol %. As in the case of previously base screening experiments, the reactions would be carried at RT and then for those with low conversion, refluxed. The ^{1}H NMR spectra was taken to each reactional mixture in order to check for product formation.



310

Entry	Catalyst	Observations[a]
1	$Rh_2(OAc)_4$	CM, SR
2	$Rh_2(tfa)_4$	CM, SR
3	$Rh_2(cap)_4$	CM, SR
4	CuI	CM, SR
5	$Cu(OAc)_2$	CM
6	$Cu(OTf)_2$	CM

[a] CM = complex mixture; SR= significative amount of substrate remaining; NC= no conversion

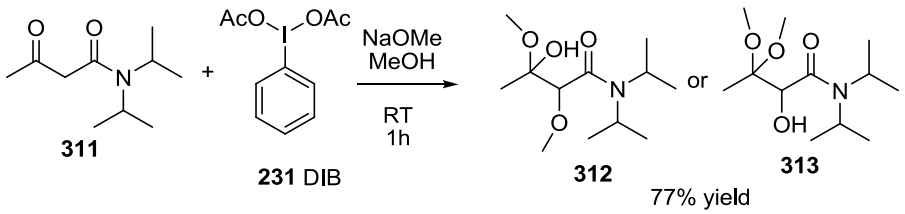
Scheme 137: Catalysts screening for metal carbenoid formation with **310**.

The reactions presented on Scheme 137 didn't afforded any product formation. With Rh-based catalysts and CuI a significative amount of substrate was unreacted. With Cu (II) catalysts the substrate was decomposed providing a complex mixture. Another similar reaction with $Cu(OTf)_2$ during 27 h at RT didn't revealed any substrate decomposition, therefore only at the reflux the substrate can be decomposed. Despite the low solubility of $Rh_2(OAc)_4$ in $C_2H_4Cl_2$ at RT complete and immediate solubilization was observed upon addition of **310**. This result indicates that the substrate can coordinate to the catalyst at axial position making it soluble, though the π-backdonation isn't strong enough to form the metal carbenoid by NHC displacement. Perhaps a C-C bond is too much strong to be broken by the Rh (II) π-backdonation and this method was also abandoned.

3.2.2. Iodine (III)-Mediated Diazo- and Transition Metal-Free C-H Insertion/C-C Bond Formation

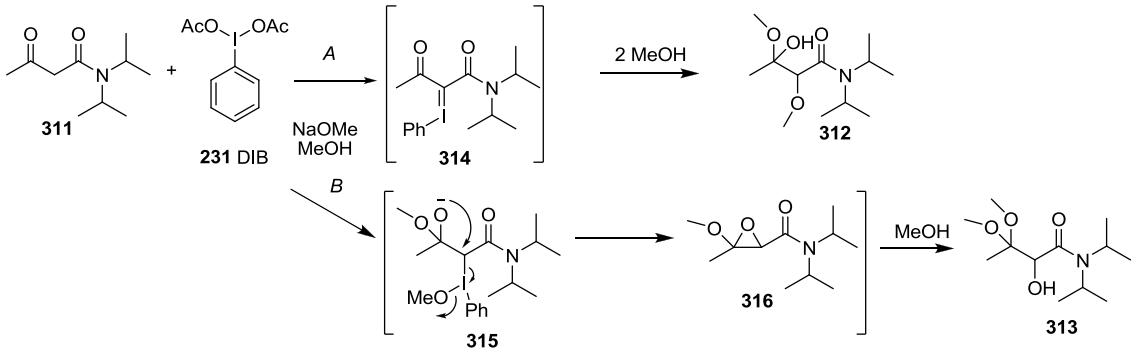
Phenylodonium ylides are recognized as diazo surrogates though they are less stable, more difficult to purify and their oxidizing properties can also decompose the Rh (II) catalyst. These ylides are usually synthesized from (diacetoxyiodo)benzene **231** (DIB) or iodosobenzene **232** (IB), which are shelf stable reagents, where diazo transfer reagents usually are the also potentially explosive azides.

Since the previous attempts failed we turned our attention for these non explosive reagents. In order to synthesize the phenyliodonium[116] of the model substrate **311** for further Rh (II)-catalyzed decomposition, the reaction with DIB and NaOMe in MeOH was carried out. After several attempts only complex mixtures were obtained. A pure product was obtained only when the reaction was carried at the cold room temperature and the workup under ice / water cold glassware. Then, instead of the expected phenyliodonium ylide product a decomposition product was obtained. It was extremely heat sensitive and only the NMR characterization was performed, although its structure was not unambiguously assigned (Scheme 138).



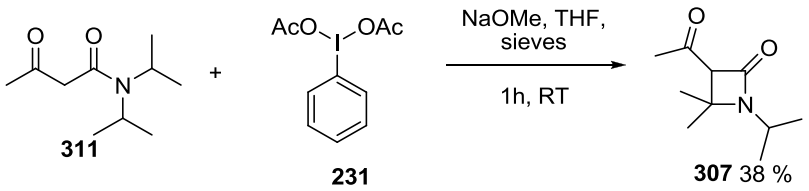
Scheme 138: Isolation attempt of iodonium ylide derived from **311**.

Two mechanisms were considered, one where the iodonium ylide **314** decomposes and the product **312** is obtained by MeOH attack on the putative carbene followed by ketal formation (Scheme 139, path *A*), or a similar mechanism to a described one[101b] (path *B*) where the intermediate **315** originates the epoxide **316** which is opened by the solvent.



Scheme 139: Two possible mechanistic pathways from where the products **312** and **313** can arise.

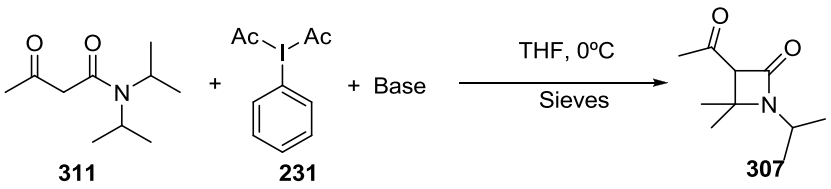
Since the product obtained by path *A* is a common protic solvent insertion on the carbene, the reaction was carried on THF (Scheme 140).



Scheme 140: One step I (III)-mediated C-H insertion with C-C bond formation.

To our delight the product of C-H insertion arose in 38 % isolated yield, without the addition of any transition metal. In order to yield improvement, several reaction conditions were screened at the Max-Planck-Institut für Kohlenforschung (Germany) on Prof. Dr. Nuno Maulide's laboratory, where the product was not isolated and the conversions were determined by ^{1}H NMR. The reaction vessels were protected from

light since the iodonium ylides are light sensitive. A substrate / reagents ratio screening was performed (Scheme 141).

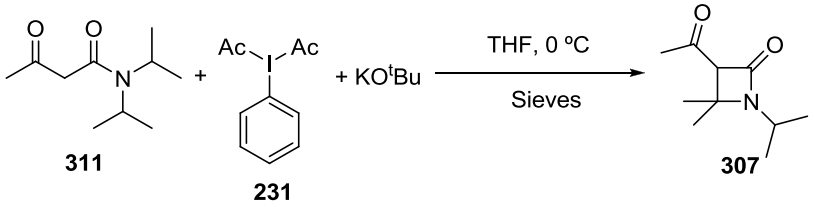


Entry	231eq.	Base (eq.)	Time (h)	307 (%)[b]	Unreacted 311 (%)[c]
1	1.1	KO^{t}Bu (2.7)	1	31	9
2	1.1	KO^{t}Bu (1.1)	1	17	16
3[a]	1.1	NaOMe (2.7)	1	27	6
4	1.1	NaOMe (2.7)	1	28	10
5	1.5	KO^{t}Bu (2.7)	1.15	34	9
6	2	KO^{t}Bu (2.7)	1	21	9

[a]Half the concetration [b]Calculated yield of product by ^{1}H NMR based on added internal standard
[c]Calculated unreacted substrate by ^{1}H NMR based on added internal standard

Scheme 141: Results obtained with the substrate / reagent ratio screening.

The reaction afforded better conversions with 2.7 eq. of KO^{t}Bu and 1.5 eq of **231**; concentration had a minimal effect on product formation and KO^{t}Bu was better suited than NaOMe. No complete substrate consumption was observed and several unidentified products were present on the reaction crude mixture, which were never isolated, despite the attempts. The effect of the reaction time at 0 ºC was performed (Scheme 142).



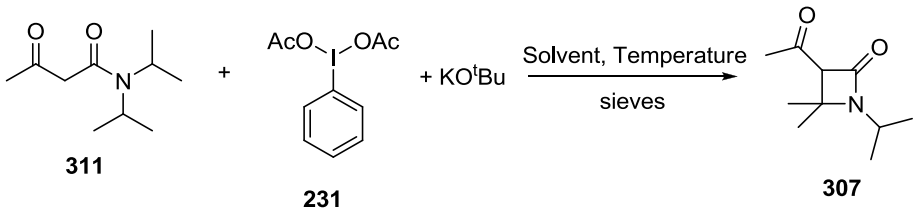
Entry	Time (h)	307 (%)[a]	Unreacted 311 (%)[b]
1	3.5	41	16
2	1	31	9

[a] Calculated yield of product by ^{1}H NMR based on added internal standard [b] Calculated unreacted substrate by ^{1}H NMR based on added internal standard

Scheme 142: Results obtained with the reaction time study at 0 ºC.

The reaction time extension to 3.5 h had a significative yield improvement, though further extension was not beneficial.

Next, a solvent screening was performed (Scheme 143).

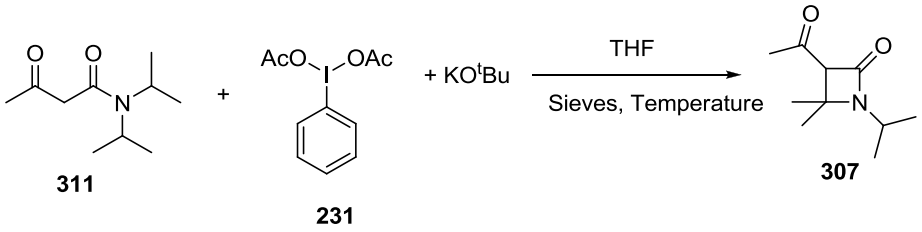


Entry	Solvent	Time (h)/ Temperature (ºC)	4Å Sieves (mg)	307 (%)[b]	Unreacted 311 (%)[c]
1	Acetonitrile	6 / 0 + 13 / RT	303	18	35
2[a]	Acetonitrile	22 / 0 + Overnight / RT	0	15	5
3	$C_2H_4Cl_2$	3 / 0	200	15	9
4	DMF	2.5 / 0	200	0	17
5	DMSO	2.5 / RT	197	8	25
6	1,4-Dioxane	2.15 / RT	200	31	6
7	Toluene	3 / 0	0	34	nd

[a] NaOMe was used as base [b] Calculated yield of product by ^{1}H NMR based on added internal standard [c] Calculated unreacted substrate by ^{1}H NMR based on added internal standard

Scheme 143: Results obtained with the solvent screening.

Several solvents were tested and no better yields were obtained and again the substrate was observed on the reaction crude mixture. A brief study of low temperatures (-30 and -78 ºC) was conducted (Scheme 144).

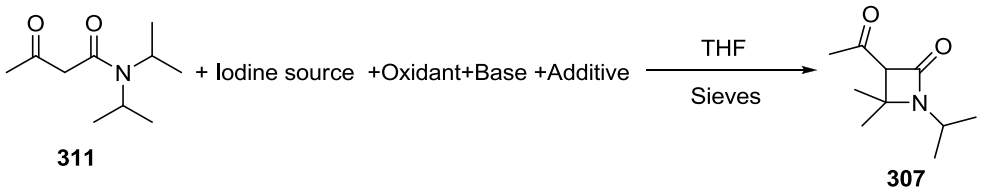


Entry	Time (h)	Temperature (ºC)	231 equivalents	307 (%)[a]	Unreacted 311 (%)[b]
1	1	-30	1.1	28	9
2	24	-30	2	25	nd
3	2	-78	1.1	25	20
4	7	-78	1.5	6	7

[a] Calculated yield of product by ^{1}H NMR based on added internal standard [b] Calculated unreacted substrate by ^{1}H NMR based on added internal standard.

Scheme 144: Results obtained with a brief low temperatures screening.

The low temperatures screening didn't afforded improved yields and again the unreacted substrate was obtained. A brief catalytic iodine / co-oxidant screening was tested as well (Scheme 145).



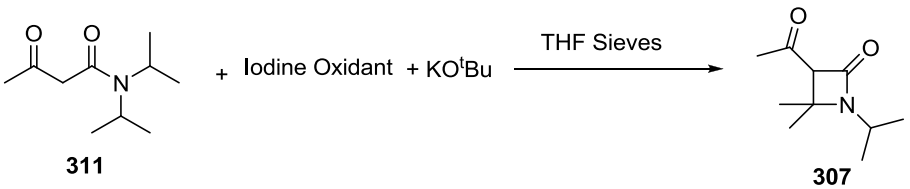
311 307

Entry	Time (h) / Temperature (ºC)	Iodine Source (eq.)	Oxidant (eq.)	Base (eq.)	Additive (eq.)	307 (%)[a]	Unreacted 311 (%)[b]
1[117]	22 / 0 + Overnight / RT	TBAI (0.2)	m-CPBA (4)	KO^{t}Bu (4)	-	0	0
2[118]	2 / 0 + Over weekend / RT	PhI (0.5)	m-CPBA (4)	Cs_2CO_3 (4)	AcOH (0.5)	0	21
3	3 / 0 + Over weekend / RT	PhI (0.5)	TBHP (5)	Cs_2CO_3 (4)	AcOH (0.5)	3	11

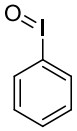
[a] Calculated yield of product by ^{1}H NMR based on added internal standard [b] Calculated unreacted substrate by ^{1}H NMR based on added internal standard.

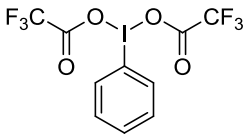
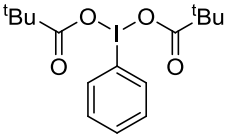
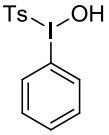
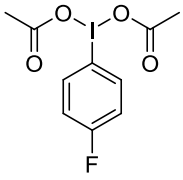
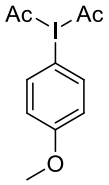
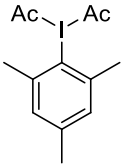
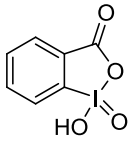
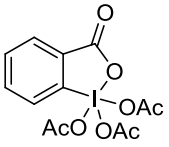
Scheme 145: Results obtained with a brief iodine / co-oxidant screening.

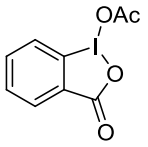
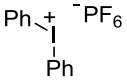
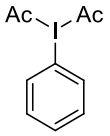
The catalytic iodine / co-oxidant attempt was unsuccessful since only trace amounts of product were obtained (Scheme 145, entry 3). In the next step, several iodine sources were also tested (Scheme 146).



311 307

Entry	Iodine Oxidant	Time / Temperature	307 (%)[a]	Unreacted 311 (%)[b]
1	 232	1 / 0	0	75

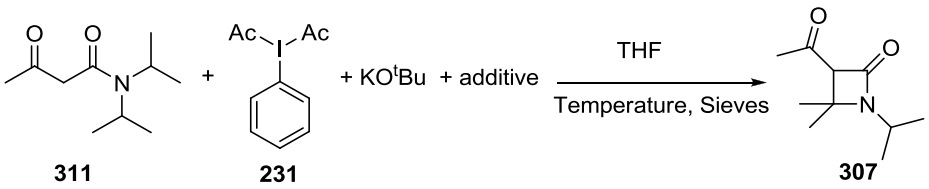
2	 **317**	1 / 0	28	16
3	 **318**	2 / 0	38	15
4	 **319**	2 / 0	30	29
5	 **320**	2.7 / 0	35	13
6	 **321**	3 / 0	23	14
7	 **322**	2 / 0	20	12
8	 **323**	3 / 0	0	71
9	 **324**	12 / 0 + Over weekend / RT	nd	nd

10	 **325**	3 / 0	0	15
11	 **326**	3.5 / 0 + 4 days / RT	0	65
12	 **231**	3 / 0	41	16

[a] Calculated yield of product by ^{1}H NMR based on added internal standard [b] Calculated unreacted substrate by ^{1}H NMR based on added internal standard.

Scheme 146: Results obtained with an iodine source screening.

From the iodine (III) sources, several different I-leaving groups didn't afforded better yields (Scheme 146, entries 1-4), as well as the substituents on the aromatic ring (entries 5-7). Iodine (V) sources were completely ineffective (entries 8 and 9) to afford the product and also the diphenyl substituent (entry 11). A brief additive screening was performed (Scheme 147).



311 **231** **307**

Entry	Additive (eq)	Time (h) / Temperature (ºC)	307 (%)[b]	Unreacted 311 (%)[c]
1	LiCl (4)	3 / 0	22	11
2	2,2,2-Trifluoroethanol (4)	3 / 0	16	12
3[a]	TEMPO (0.2)	6 / 0+ Over weekend / RT	10	nd
4	none	3 / 0	41	16

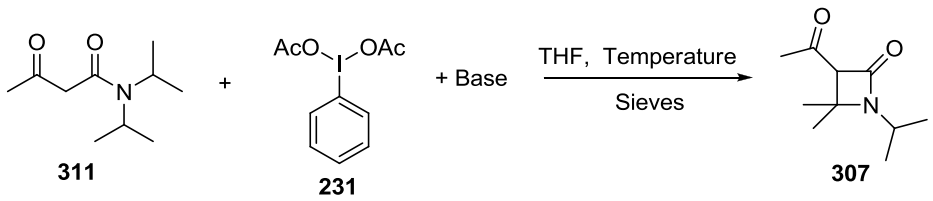
[a] No base was used and the TEMPO was added in portions, 0.1 eq. in the beginning and 0.1 eq. 4 hours later [b] Calculated yield of product by ^{1}H NMR based on added internal standard [c] Calculated unreacted substrate by ^{1}H NMR based on added internal standard

Scheme 147: Results obtained with a brief additives screening.

On the screening where additives were employed, the LiCl which could complex the 1,3-dicarbonyl compound afforded a decreased yield of **307**; 2,2,2-trifluoroethanol is known to replace the acetate ligands on the iodine (III)[101a] but its use had a negative

effect on product yield. The radical inducer reagent TEMPO was used but only a small conversion was obtained over a prolonged reaction time.

A base screening was also performed (Scheme 148).



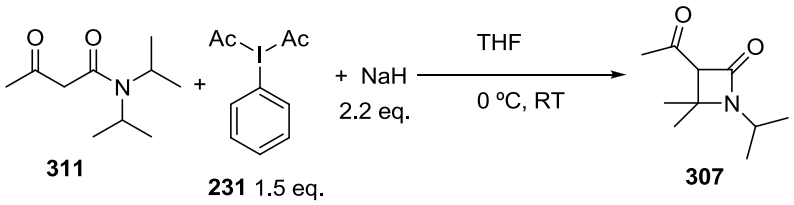
Entry	Time (h)/ Temperature (ºC)	Base (eq)	307 (%)[c]	311 (%)[d]
1[a]	0.66 / RT	DBU (2.5)	0	0
2	1 / RT	KOH (2.5)	0	0
3	1 / 0	NaOMe (2.7)	27	6
4	3.5 / 0	KO^{t}Bu (2.7)	41	16
5	3 / 0	KO^{t}Bu (2.4)	29	11
6	4 / 0 + 15 / RT	Cs_2CO_3 (2.7)	31	19
7	2 / 0 + 15 / RT	MgO (2.7)	0	0
8	3 / 0	NaO^{t}Bu (2.7)	38	4
9	3 / 0	LiO^{t}Bu (2.7)	17	6
10	2.15 / 0	NaO^{t}Bu (2.7)	27	4
11[b]	3 / 0	KO^{t}Bu (2.7) + H_2O (1.9)	41	nd
12	3 / 0	NaH (2.2)	45	nd

[a] Dichloromethane (2mL) was used as solvent [b] H_2O was added after the base [c] Calculated yield of product by ^{1}H NMR based on added internal standard [d] Calculated unreacted substrate by ^{1}H NMR based on added internal standard.

Scheme 148: Results obtained with a base screening.

Several bases were tested where NaO^{t}Bu afforded less unreacted substrate amount than KO^{t}Bu (Scheme 148, entries 4 and 8). When H_2O was employed to form *in situ* small KOH particles[119], the conversion was also improved, but NaH was the best base tested since it afforded **307** in 45 % conversion without detected unreacted substrate.

Since none of the previous screenings afforded good yields, the reaction was divided in two steps, one at 0 ºC for the iodonium ylide formation and another at a higher temperature for its decomposition and the sieves were discarded since no yield improvement was found (Scheme 149).

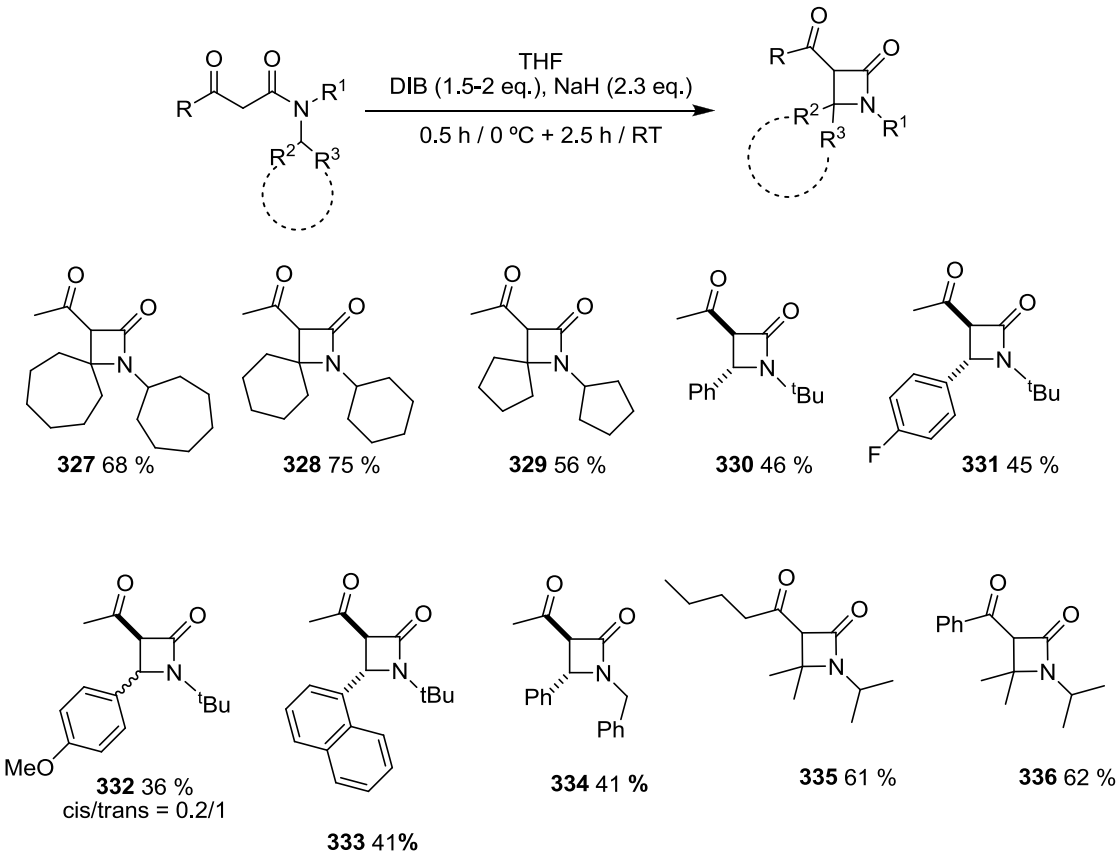


Entry	Time at 0ºC	Time at RT (h)	Isolated 307 (%)[e]	307 (%)[f]
1	1h	2	53	-
2	0.5h	2.5	66	-
3	0.25h	2.75	-	68
4	1min	3.5	-	55
5 [a]	0.5h	1.5	-	66
6 [b]	0.5h	2.5	69	-
7 [c]	0.5h	2.5	68	-
8 [c, d]	0.5h	2.5	71	-

[a] 30 ºC was used as 2nd temperature [b] 10 ºC was used as 2nd temperature [c] 17 ºC was used as 2nd temperature [d]5x reaction scale [e] Isolated yield by column chromatography [f] Calculated yield of product by ^{1}H NMR based on added internal standard.

Scheme 149: Results obtained with on the final reaction temperature screening.

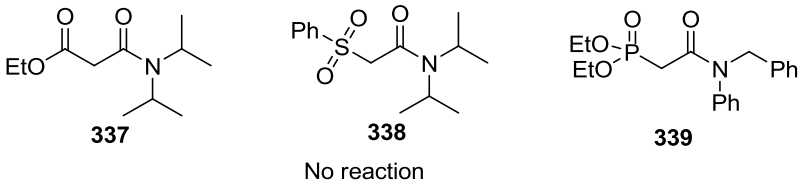
Only with the two step temperatures procedure the isolated product yield reached 69 % of **307** (Scheme 149, entry 6). The reaction also endured a 5x scale up where a good yield (71 %) was finally obtained (entry 8). With these optimized conditions in hand a substrate scope was conducted (Scheme 150).



Scheme 150: Scope of the iodine (III) mediated C-H insertion.

The substrate scope was performed with cyclic N-substituents where rings of seven, six and five members and it afforded the spiro β-lactams **327**-**329** which were obtained in up to good yields (Scheme 150). The unsymmetrical N-substituents, afforded moderate yields where the benzylic positions were evaluated containing electrondonating and electronwithdrawing groups, providing the β-lactams **330**-**333** in moderate yields and without a very significative yield distinction (36-46%). The reaction also endured the substitution on the acyl group, by such as alkanoyl (**335**) and benzoyl (**336**) which were well tolerated, despite the slight yield decrease. The DIB eq. used varied from 1.5 to 2 to have complete substrate consumption and the ylide decomposition temperature also influenced the products yield.

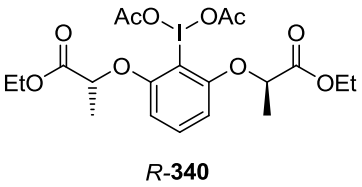
Other α-substituents were tested (Scheme 151).



Scheme 151: Other α-substituents tested.

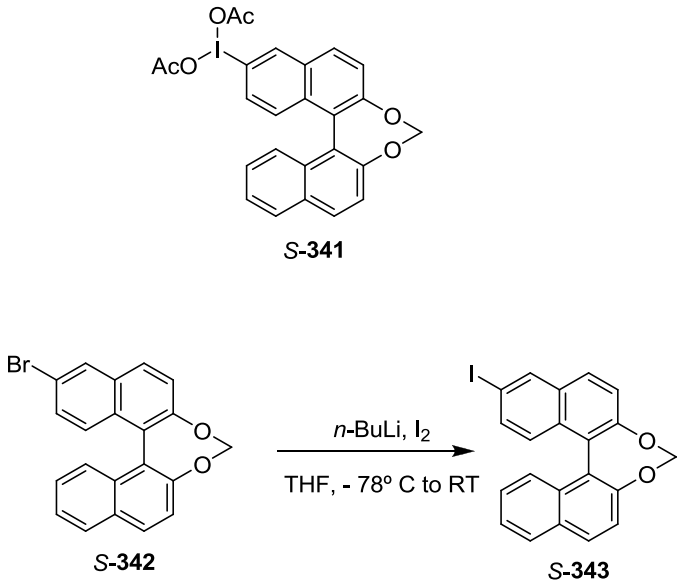
The reaction with substrates **337**-**339** where the acetyl α-substituent was replaced didn't afforded substrate consumption, narrowing the scope at this position.

An asymmetric version of the reaction was also tried. The chiral I (III) reagents[120] available usually have O nearby the I center which in this case would probably react with the putative carbene intermediate forming an ylide, diverting the path of the C-H insertion reaction (Scheme 152).



Scheme 152: Common I (III) chiral reagents.

The attempt to synthesize the probably suitable chiral iodine (III) reagent *S*-**341** wasn't successful since on the several attempts to substitute the Br for I on *S*-**343**, the product with an H substitution was also produced in appreciable yield (Scheme 153). The several attempts to separate them also failed, since they have a similar polarity. On the next reaction to convert *S*-**343** into *S*-**341** by oxidation with $NaIO_4$ severe degradation with I liberation was also observed with a low convertion on *S*-**341** therefore this synthesis was discarded.



Scheme 153: Chiral iodine (III) compound synthsis.

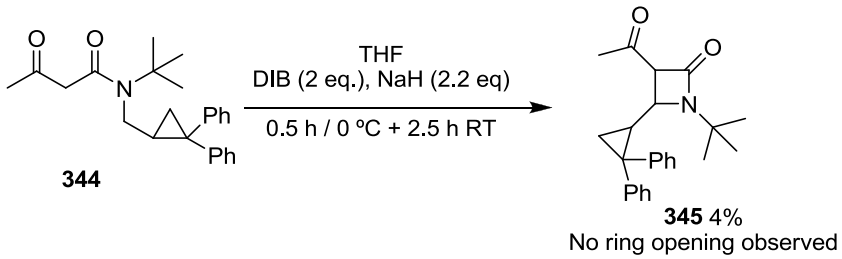
The β-lactams **307**, **327**-**336** were evaluated for biological activity assays on collaboration by Prof. Patrícia Rijo from Universidade Lusófona / iMed.UL. The microorganisms used in this study were obtained from the American Type Culture Collection (ATCC). They included three Gram-positive bacteria (**S.a.** - *Staphylococcus aureus* ATCC 25923, **E.f.** - *Enterococcus faecalis* ATCC 29212, and **M.s.** - *Mycobacterium smegmatis* ATCC 607), two Gram-negative bacteria (**E.c.** - *Escherichia coli* ATCC 25922 and **P.a.** - *Pseudomonas aeruginosa* ATCC 27853) and a yeast (**C.a.** - *Candida albicans* ATCC 10231). Microorganisms were grown at 37 ºC in Muller-Hinton culture media. All compounds showed diameters of the inhibition zones of 5 mm, as the negative control, therefore the β-lactam compounds were inactive against all the microorganisms tested.

In conclusion, the method developed doesn't employ transition metals or diazo compounds, besides the reactive phenyliodonium intermediate is generated at 0 ºC and consumed *in situ* under smooth temperatures. Only when this two step temperatures approach was carried the **307** conversions rose above 45 % and a substrate scope tolerates motif variations with good yields. No chromatographic purification of the activated substrate is required and the (diacetoxyiodo)benzene **231** is a shelf stable reagent.

3.2.3. Study of the Mechanism of Iodine (III)-Mediated C-H Insertion/C-C Bond Formation

After the reaction optimization, we turned our attention to disclose the reaction mechanism considering that the observed C-H insertion may occur via radical and/or carbene pathways. From the range of optimization and the preparative isolation experiments (Scheme 149, entry 8 and Scheme 150), apart of the desired C-H insertion products **307**, **327**-**336**, none secondary product was isolated which could have provided valuable mechanistic insights. Therefore several substrates were synthesized and the reactions were performed without yield optimization.

The substrate **344** was synthesized containing the 2,2-diphenylcyclopropyl group which is commonly used as radical probe due to the high ring opening constant if a radical is present on the adjacent methyl group[121] (Scheme 154).

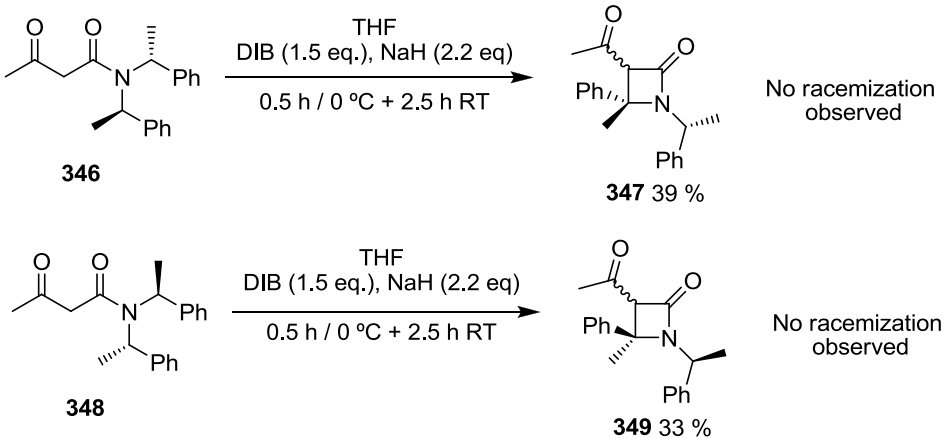


Scheme 154: I (III)-mediated C-H insertion on a methyl 2,2-diphenylcyclopropyl group.

The iodine (III) mediated C-H insertion on substrate **344** (Scheme 154) furnishes a complex mixture where no cyclopropane ring-opening product was observed and the C-H insertion product **345** was obtained with the intact ring, albeit in low yield (4%).

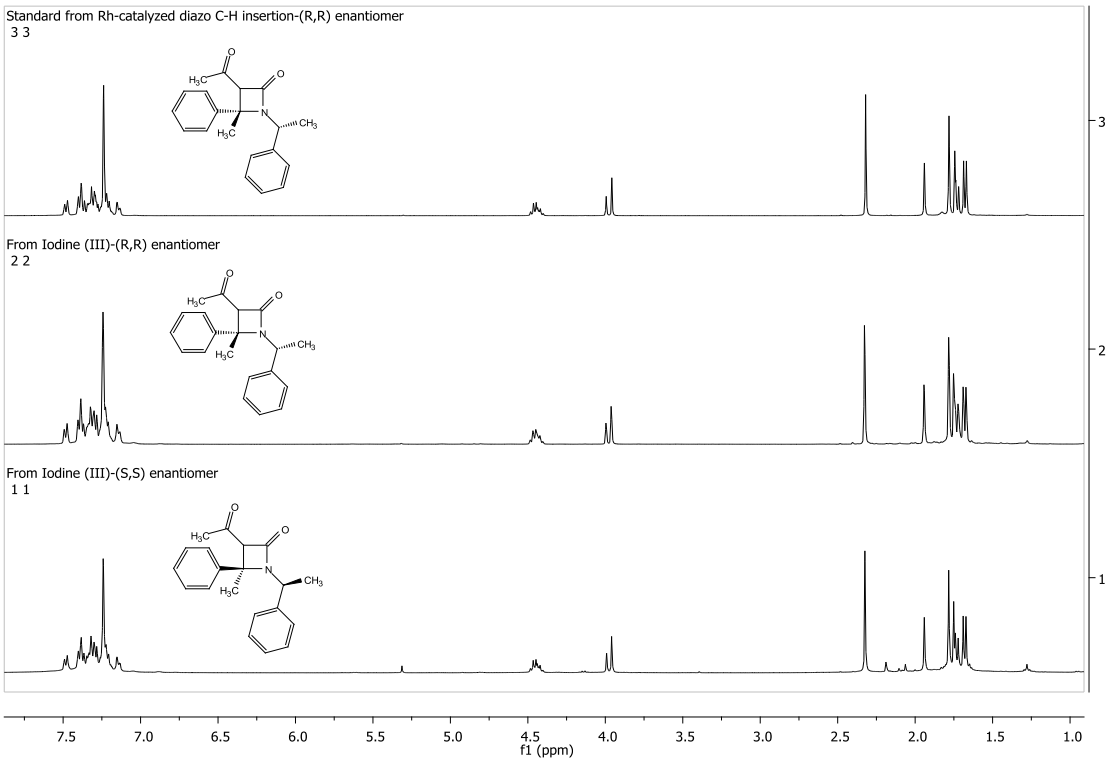
More conclusive indication which can exclude a radical pathway was obtained by the insertion on chiral C-H bonds. The singlet carbene insertion on C-H bonds proceeds with full retention of configuration whilst a radicalar mechanism or triplet carbene should afford at least partial racemization[122]. Thus, enantiomerically pure substrate **346** and its enantiomer **348** were synthesized (Scheme 155). These diastereomers simplify the analysis since if any racemization occurs, the observed achiral compound would be *meso* and therefore with different NMR spectrum. The respective diazo compounds were also synthesized as well as the *meso* compound and subject to $Rh_2(OAc)_4$ catalysis

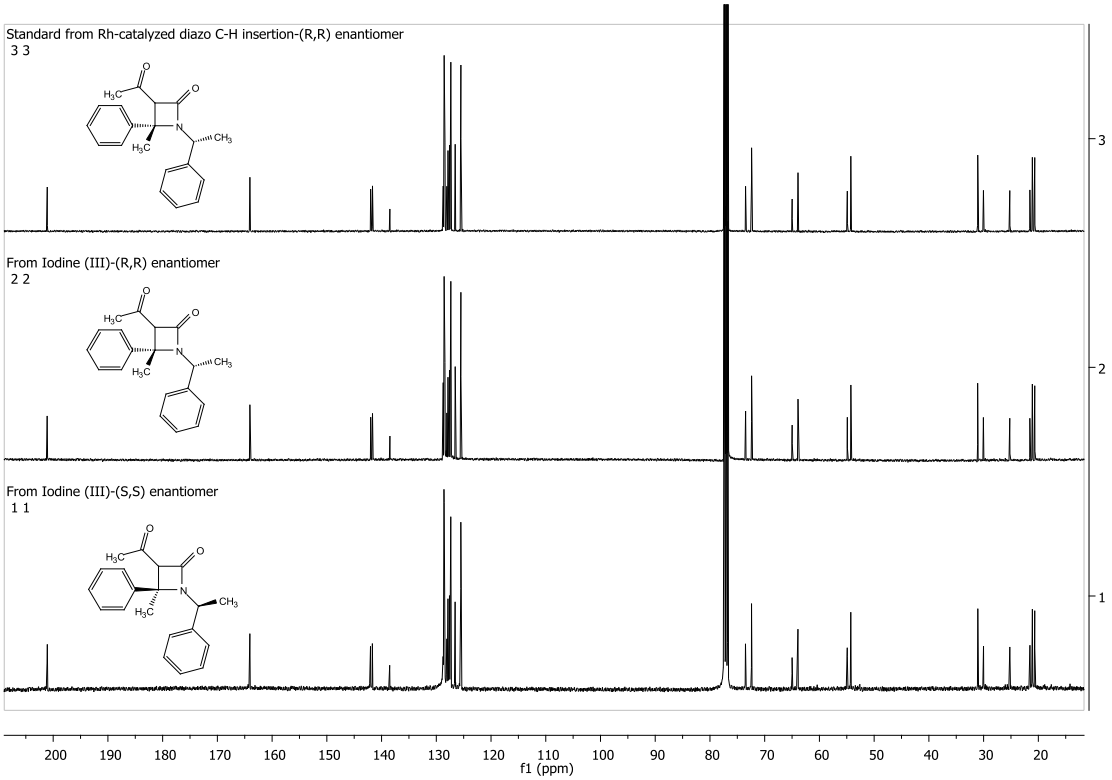
under standard conditions for product comparison, since the C-H insertion with Rh (II) carbenoids produce the product with full retention of configuration[28].



Scheme 155: I (III)-mediated C-H insertion on chiral centers.

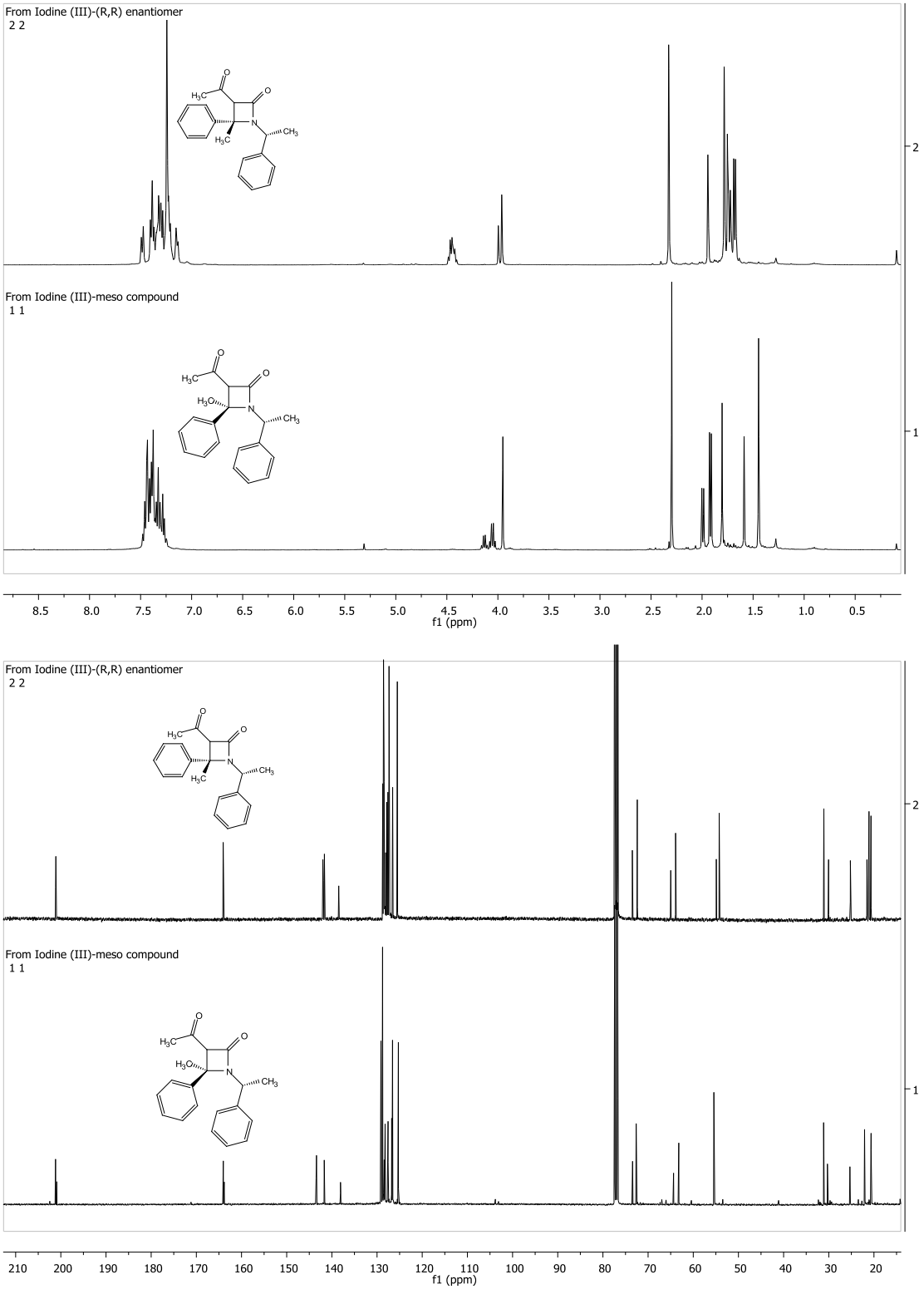
The ^{1}H and ^{13}C NMR spectrum of products **347** and **349** were identical for both I (III)-mediated C-H insertions and the $Rh_2(OAc)_4$-catalyzed respective diazo decomposition which have also the same d.r. of 2:1 (Scheme 155 and Scheme 156).





Scheme 156: ^{1}H and ^{13}C NMR (400 MHz, $CDCl_3$) comparison between the obtained from $Rh_2(OAc)_4$-catalyzed diazo C-H insertion (up) and from the iodine (III) mediated C-H insertion (middle and down)-chiral coumpounds.

The reaction with the enriched *meso*-compound was also performed with both Rh-(II)-catalyzed diazo decomposition and I-(III) mediated C-H insertion. As expected, the chiral and *meso* derived products had a different ^{1}H and ^{13}C NMR spectrum. No peaks corresponding to the *meso*-compound were observed on the chiral iodine (III) mediated reactions (Scheme 157).

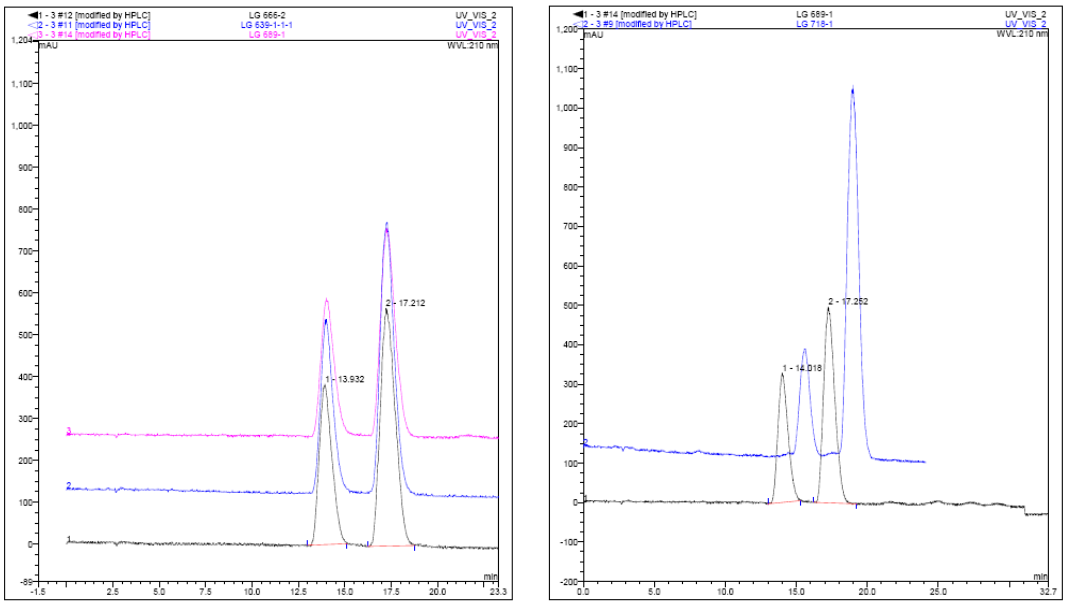


Scheme 157: ^{1}H and ^{13}C NMR (400 MHz, $CDCl_3$) comparison between the iodine (III) mediated C-H insertion on the chiral compound (up) and the *meso* derived compound (down).

The products were also analyzed by RP-HPCL and again no racemization on the C-H insertion was observed on the chiral compounds **347** and **349** (Scheme 158). The peaks of the product obtained by $Rh_2(OAc)_4$-catalyzed diazo decomposition were

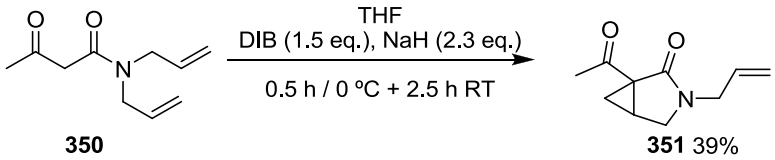
completely superimposed with the obtained for both enantiomers of the I (III) mediated C-H insertion (left).

Since the successive chromatographic purifications of the *meso* amine, precursor of the meso substrate, could not afford it pure but always with traces of the chiral amine. Therefore the Rh-catalyzed diazo decomposition with the enriched *meso* compound also afforded traces of the chiral product, only detectable by RP-HPLC, as it can be seen on Scheme 158, right, up chromatogram. The peak separation had good resolution (R_t=13.9 min. and 17.2 min. for the chiral compounds **347** and **349** and R_t= 15.6 min. and 19.0 min. for the *meso* compound). By NMR and HPLC no racemization on the C-H insertion was found which can exclude a radicalar mechanism or a triplet carbene; the I (III)-mediated C-H insertion with C-C bond formation therefore proceed via a singlet carbene.



Scheme 158: RP-HPLC (C-8, 50% CH_3CN in H_2O, λ=210 nm, 1 mL/min) overlay chromatograms for comparison. Left: the $Rh_2(OAc)_4$ catalyzed diazo C-H insertion ((R,R) enantiomer, middle) and the obtained with the iodine (III) mediated C-H insertion ((R,R) enantiomer **347**, up; (S,S) enantiomer **349**, down). Right: the $Rh_2(OAc)_4$ catalyzed *meso*-enriched diazo C-H insertion (up) and the obtained with the iodine (III) mediated chiral C-H insertion ((R,R) enantiomer down).

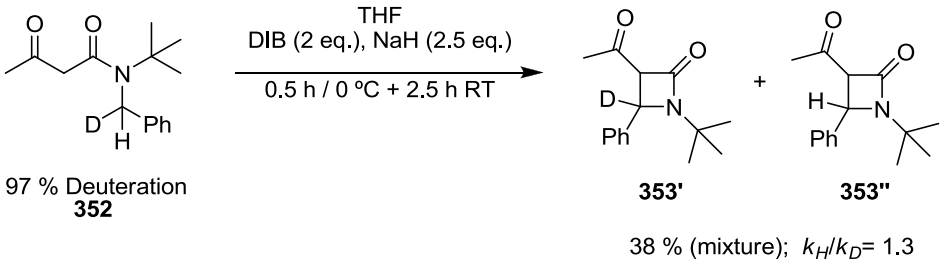
Being olefin cyclopropanation another feature of the dirhodium (II) carbenoids, (though radicalar mechanisms are also known[123]), this reaction was also carried out under the optimized conditions (Scheme 159).



Scheme 159: I (III)-mediated cyclopropanation.

As expected the cyclopropane ring **351** was obtained, although in moderate yield (39 %).

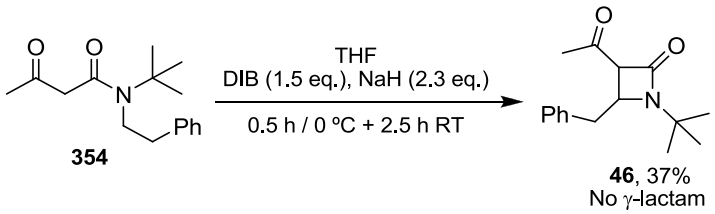
A competitive experiment with a monodeuterated substrate **352** was carried under the optimized conditions. The deuterium incorporation on **352** was determined to be 97 % by HRMS (Scheme 160).



Scheme 160: I (III)-mediated competitive experiment with H *vs* D migration.

Since the product 1,3-dicarbonyl's α position is labile, fully deuteride replacement by proton was found by ^{1}H NMR only on the migrating deuteride (compound **353''**) and the kinetic isotopic effect (KIE) was calculated based on the non-labile *N*-amide's α proton / deuterium, HRMS was also used. The product mixture was obtained in 38 % yield and the KIE value found was 1.3 for both techniques which is within recorded experimental KIE values[124] for the intramolecular insertion with Rh (II) based catalysts on diazo reactions (KIE = 1.1-1.6) on a C-H bond adjacent to a nitrogen and near the obtained for Cu (I) catalysts (1.5-3.1). Hence, here the C-H insertion is not involved in the rate-determining step of the overall process.

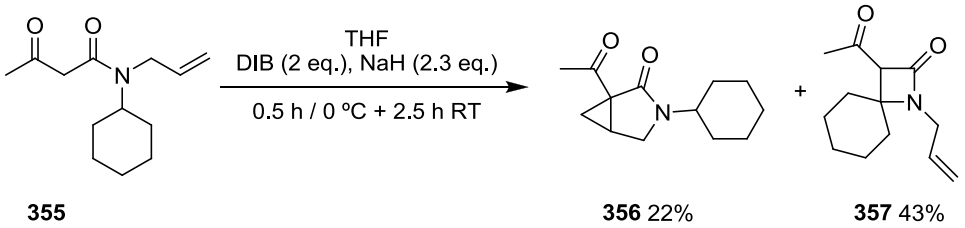
The dirhodium (II)-catalyzed C-H insertion on the diazo parent of substrate **354** is known for Rh(II)-based catalysts with different electronic profiles[39] and different β-/γ-lactams proportion are obtained in which for more electrofilic catalysts more β-lactam is formed due to the Rh-carbenoid instability (Scheme 161).



Scheme 161: I (III)-mediated competitive experiment between β–/γ–lactams formation.

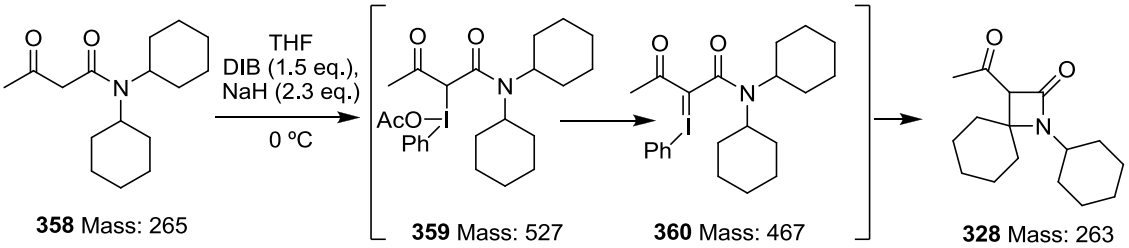
With substrate **354**, the reaction was carried out under the iodine (III) optimized conditions and the selectivity towards the β-lactam **46** (37 %) was complete and no γ-lactam was observed by ^{1}H NMR on the reaction mixture. Therefore the generated carbene is highly unstable.

Müller and Fernandez studied the dirhodium (II) catalyzed C-H insertion *vs* cyclopropanation to compare iodonium and diazo compounds[104]; identical product ratio was obtained, which was considered to support a common complexed carbenoid intermediate. The cyclopropanation product was favored ca. 3:1. When a similar competing reaction was performed with substrate **355** under our optimized conditions, the C-H insertion product **357** was preferential with 43 % isolated yield and 22 % of the cyclopropanation product **356** were obtained (Scheme 162).

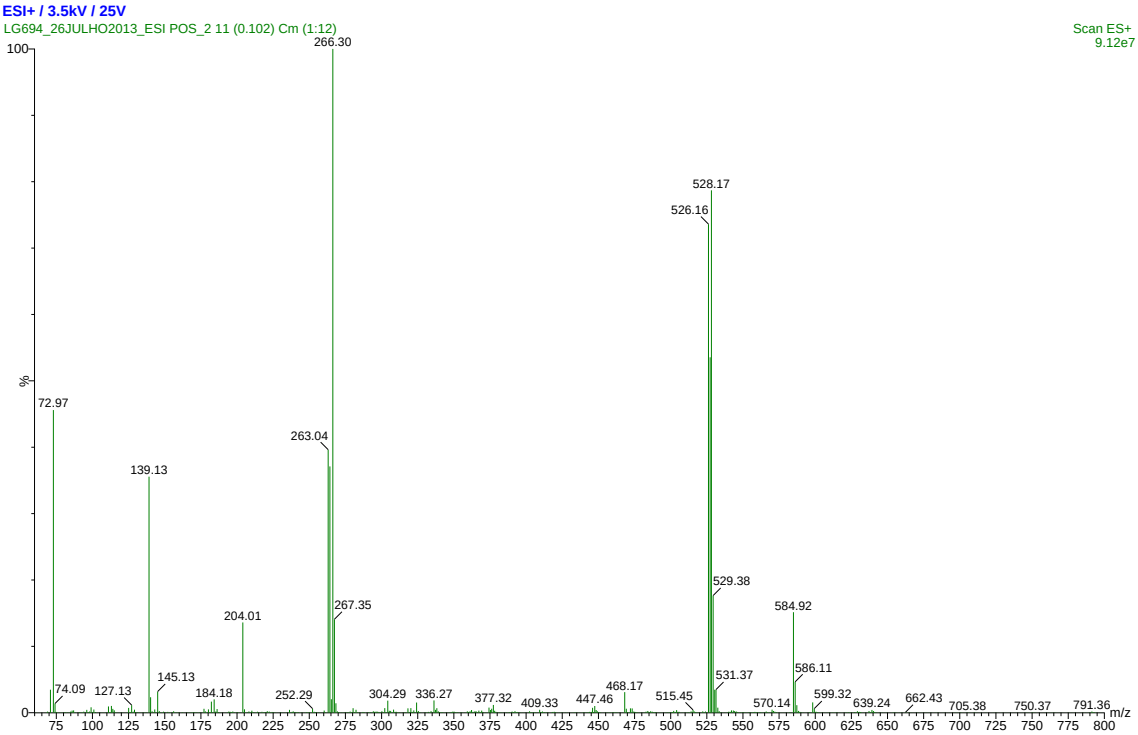


Scheme 162: I (III)-mediated competitive experiment between C-H insertion *vs* cyclopropanation.

To gain further evidence over the iodonium ylide formation, the reaction evolution was followed by mass spectrometry (ESI-LRMS^{2}- peak deviation ± 1). The reaction with **358** (Scheme 163) was selected and an aliquot was taken in the beginning of the reaction (Scheme 164) which exhibits peaks corresponding to **358** (m/z=266-main peak), the intermediate **359** (m/z= 526,527,528), precursor to the iodonium ylide and the product **328** (m/z = 263). Several fragments of these compounds were obtained on the ms^{2} spectra.

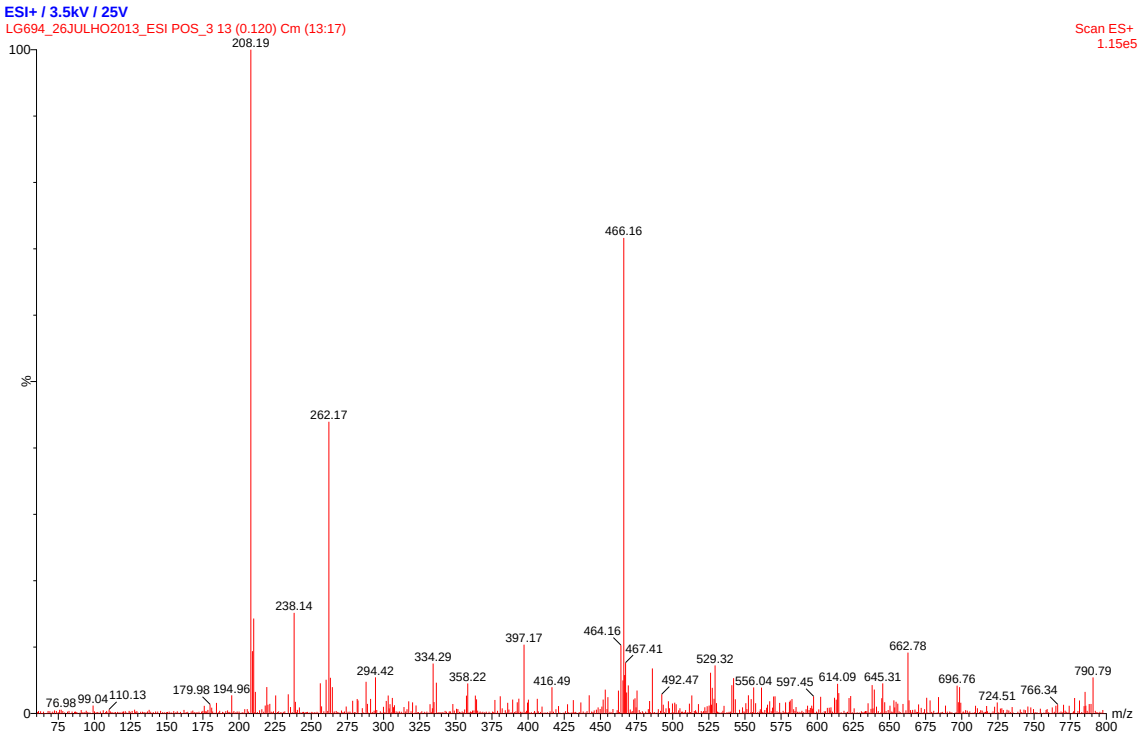


Scheme 163: Observed peaks by following the reaction of **358** by ESI-LRMS^2.



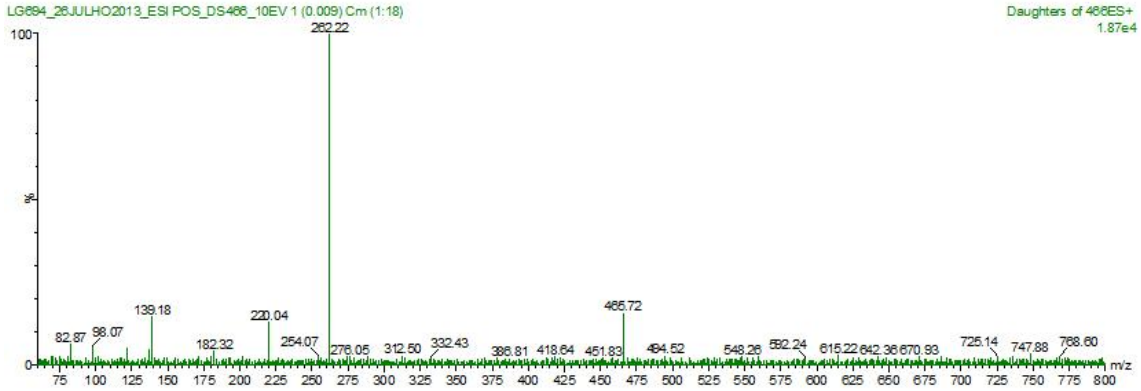
Scheme 164: Initial ESI-LRMS spectra of the reaction evolution with substrate **358**.

After ca. 30 min at 0 ºC another aliquot was taken (Scheme 165). Here the substrate **358** and the intermediate **359** were consumed since only minor peaks were found and a peak corresponding to the iodonium ylide **360** (found m/z=466) was found; the product's peak was also present (found m/z = 262).



Scheme 165: ESI-LRMS spectra of the reaction evolution after ca. 30 min. with substrate **358**.

The ms^2 spectra of the iodonium ylide peak (m/z=466, Scheme 166) afforded a peak with m/z= 262, which is in good agreement with the product or the free carbene (mass= 263).



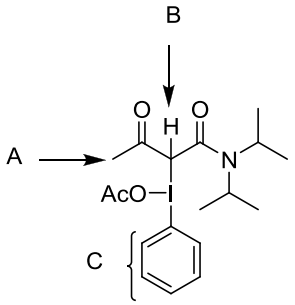
Scheme 166: ESI-LRMS^2 (peak m/z=466) spectra of the reaction evolution after ca. 30 min. with substrate **358**.

A peak corresponding to the iodonium ylide was found for substrate **358** after 30 min at 0 ºC, which was also the optimized time required to have an improved product yield (Scheme 149).

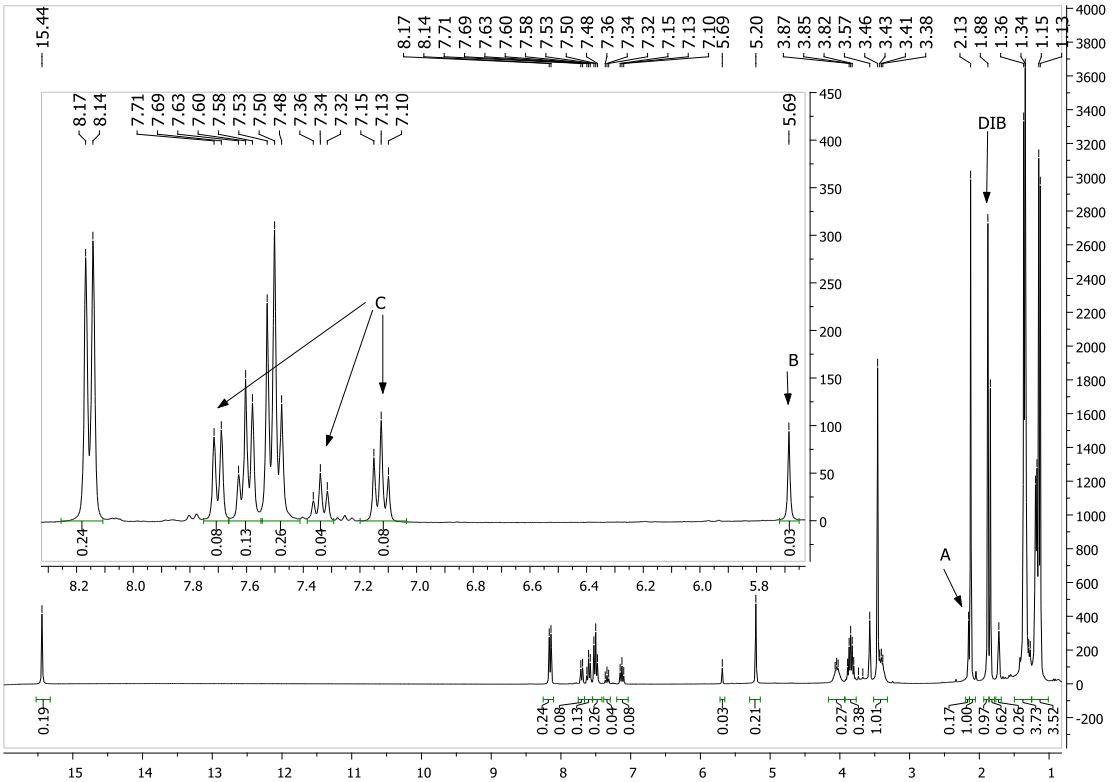
The reaction was also followed by ^{1}H NMR in dry and degassed THF-d_8 at 0 ºC with substrate **311** where the reagents were added on sequence. When DIB was added to the

substrate the peaks A, B and C (Scheme 167) were formed which can correspond to the intermediate **361**. The remaining non assigned peaks on Scheme 167 are from the keto-enol substrate's equilibrium and from DIB.

Upon addition of the NaH the reaction mixture turned very opaque and with hydrogen bubbling which prevented the acquisition for a long period of time. When it was possible, despite the low resolution, only product peaks and iodobenzene were identified as well as some remaining substrate since DIB was not completely soluble at the high experiment concentration. The phenyliodonium intermediate was not identified.



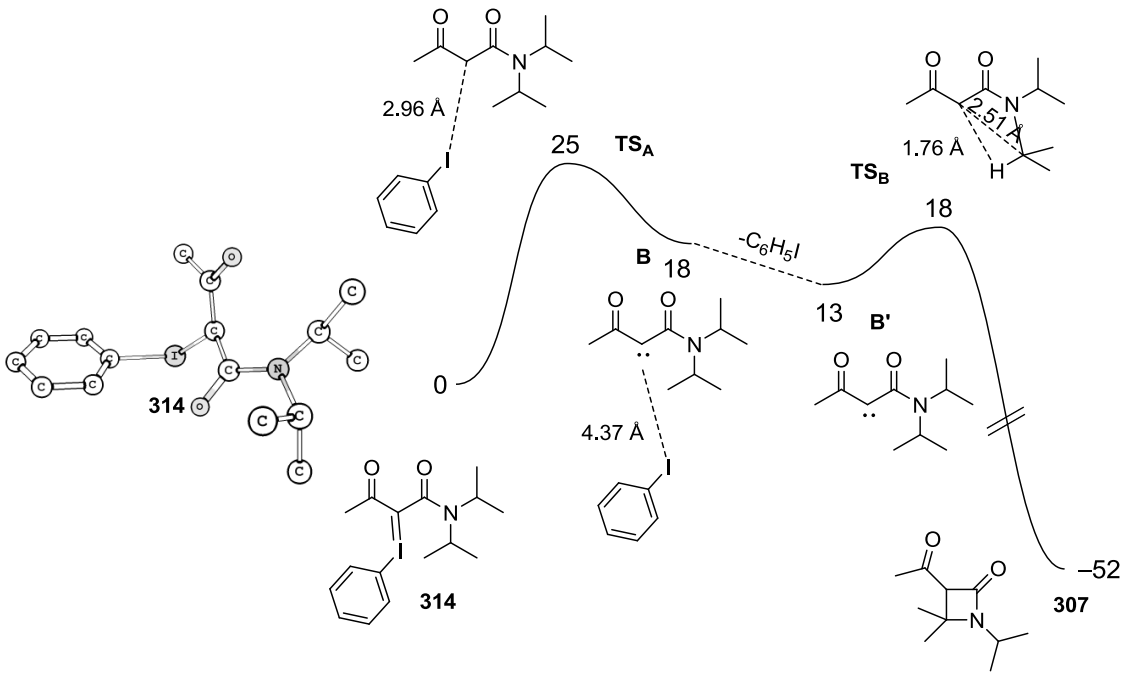
361



Scheme 167: Reaction with **311** followed by ^{1}H NMR in dry THF-d_8 at 0ºC (300 MHz).

The reaction was further studied by means of DFT calculations on collaboration with Prof. Dr. Luís Veiros. All calculations were performed using the GAUSSIAN 09 software package[125], and the M06-2X functional, without symmetry constraints. The optimized geometries were obtained with the basis set augmented with a d-polarization function for I, and a standard 6-31G+(d,p) for the remaining elements. Frequency calculations were performed to confirm the nature of the stationary points, yielding one imaginary frequency for the transition states and none for the minima. Each transition state was further confirmed by following its vibrational mode downhill on both sides and obtaining the minima presented on the energy profile. Single point energy calculations were performed using an improved basis set (basis b2) and the geometries optimized at the M06-2X/b1 level. Basis b2 consisted of a standard 3-21G augmented with a d-polarization function for I-atoms and a standard 6-311++G(d,p) for the remaining elements. Solvent effects (THF) were considered in the M06-2X/b2//M06-2X/b1 energy calculations using the Polarizable Continuum Model (PCM).

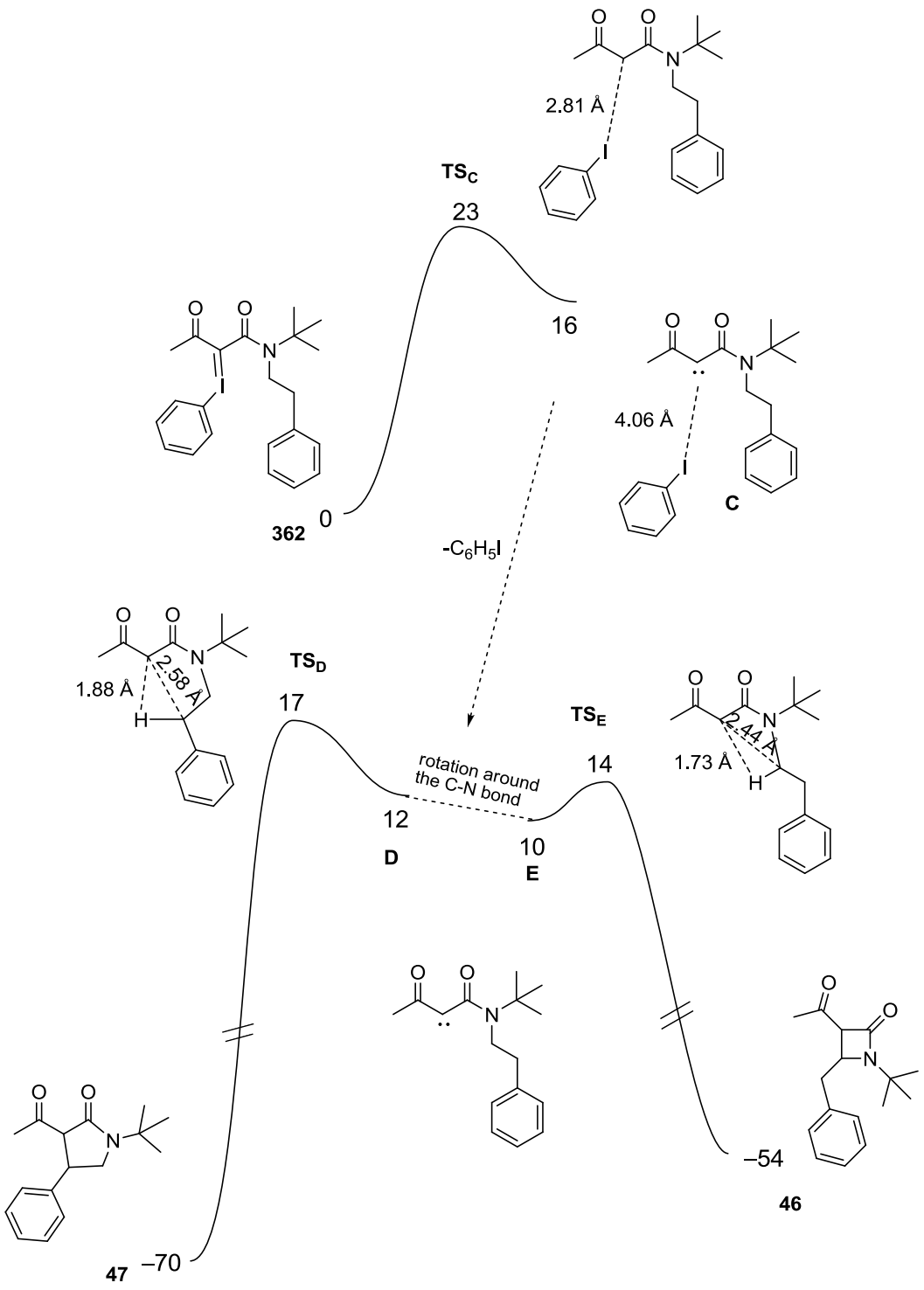
The phenyliodonium ylide was the starting point since the literature overview and the ESI-LRMS^2 results pointed to its formation. The reaction starts with loss of PhI from the iodonium ylide derived from substrate **311** (**314**, Scheme 168) resulting in the formation of the corresponding carbene, **B/B'**. In the transition state, $\mathbf{TS_A}$, the C–I bond is practically broken with a distance of 2.96 Å. This step has an energy barrier of 25 kcal mol^{-1}, being the highest of the mechanism and indicating that carbene formation is the rate limiting step. The spin state of the carbene was also studied and interestingly, the singlet carbene **B'** is more stable than its triplet form by ΔG = 4 kcal mol^{-1}, in good agreement with the insertion experiments on chiral bonds (Scheme 155).



Scheme 168: Free energy profile (kcal mol^{-1}) calculated for the formation of lactam **307**. The energy values referred to the initial iodonium ylide **314** and relevant distances are presented (Å), H omitted.

Once formed, carbene **B'** overcomes a barrier of only 5 kcal mol^{-1} and forms the final lactam **307**, in the second step of the mechanism. The transition state, **TS$_B$**, is a rather early one with only incipient C–C and C–H bond formation as shown by the long bond distances (2.51 and 1.76 Å, respectively).

The regioselectivity of the reaction was also investigated through the calculations, comparing β-lactam **46** with γ-lactam **47** formation in the case of substrate **354** (Scheme 161 and Scheme 169). Again from the phenyliodonium intermediate **362**, the carbene formation has an energy barrier of 23 kcal mol^{-1}, being also the rate limiting step of the mechanism. Then the rotation around the C-N bond can afford both β- or γ-lactams, where the β-isomer **46**, although being less stable by 16 kcal mol^{-1}, has a barrier of 3 kcal mol^{-1} lower than the γ-isomer **47**, being that the only product experimentally observed.



Scheme 169: Free energy profile (kcal mol^{-1}) calculated for the formation of β-lactam **46**. The energy values referred to the initial iodonium ylide **362** and relevant distances are presented (Å).

All the evidences gathered by studding the mechanism pointed to a singlet carbene involvement since the insertion on chiral bonds has complete retention of configuration and no ring opening products from substrate **344** were detected. As a typical carbene intermediate the reaction can also afford olefin cyclopropanation products, but a preference for C-H insertion was found with substrate **355**. A competitive C-H/D

insertion experiment with the monodeuterated substrate **352** displays a KIE near the unit which suggests that the C-H insertion step is not the rate limiting one. Instead the DFT calculations point the carbene formation as the rate limiting step and on a competitive insertion with β- or γ-lactam formation the kinetic β-lactam product was preferential which is also according the experimental observations. By following the reaction with ESI-LRMS^2 the phenyliodonium **360** mass was observed as well as its precursor **359**.

3.3. Conclusions

The C-H insertion reaction with C-C bond formation is nowadays dependent of the diazo substrates as well as dirhodium (II) catalysts. This reaction has a growing importance on the common laboratory synthesis since it can short the retrosynthetic plans while activating alkane C-H bonds. Despite the many possible applications this tool is not used on large scale applications, not because the catalyst high cost since this can be circumvented by its recover, but because the diazo compounds explosive profile, as well as their azides precursors. Such risk can't be tolerated on industrial plants and many efforts are being conducted to reach a viable option.

With the objective to find a safe and practical alternative to the diazo's functional group for the C-H insertion reaction with C-C bond formation, several options were tested. Sulfonium ylides proved to be too much stable for dirhodium (II) carbenoid formation, although they can react with alkynes in the presence of gold (I) catalysts to form similar products but not through a carbenoid pathway. α-Halogenated 1,3-dicarbonyl compounds also lack the desired reactivity when subjected to bases and no catalyst is necessary for their decomposition. Then, a N-heterocyclic carbene unit was evaluated as diazo surrogate but the C-C bond with the substrate is probably too strong to be broken by the dirhodium π-backdonation. When the known phenyliodonium ylides were tested an unprecedented C-H insertion reaction with C-C bond formation occurred at RT from the inactivated substrate, where the iodonium ylide was generated and consumed *in situ*. A long reaction optimization afforded the product in good yields and a substrate scope was also performed. Then the study of this mechanism supported the involvement of a singlet carbene by both experiments and DFT calculations. The highly reactive carbene also afforded typical olefin cyclopropanation products.

Therefore with the iodonium ylide *in situ* formation and decomposition method for C-H insertion with C-C bond formation here developed, the initial objective as performed even without a transition metal catalyst and with one less synthetic step.

4. CONCLUSIONS

The complexes $Rh_2(OAc)_4$(IPr) and $Rh_2(OAc)_4$(SIPr) were evaluated as catalysts for the decomposition of α-diazoacetamides. These complexes have an monocoordinated NHC at a $Rh_2(OAc)_4$ axial position, which modifies this complex reactivity. With these $Rh_2(OAc)_4$NHC catalysts the reaction times were usually longer which is explained by the decreased electrophilicity of the other Rh center. A new product can be obtained in a competitive reaction with the usual C-H insertion product. This decarbonylated product derived from the Wolff rearrangement and can be observed by combination of the α-substituent and bulky N-substituents. On competing insertion reactions between C-H bonds to form β- or γ-lactams these catalysts have a higher preference for β-lactam formation, when compared to $Rh_2(OAc)_4$. Despite the difference between the catalysts $Rh_2(OAc)_4$(IPr) and $Rh_2(OAc)_4$(SIPr) is only a saturated bond on this one, the reactivity of $Rh_2(OAc)_4$(IPr) is more distinct than and $Rh_2(OAc)_4$(SIPr) since more β-lactam is obtained and the Wolff rearrangement product. The reaction mechanism where the decarbonylated product is obtained was studied by DFT calculations, which also shows the electronic different profile. This subtle electronic effect is also verified on $Rh_2(OAc)_4^{Cl}$(IPr). Unlike the previous $Rh_2(OAc)_4$NHC complex reported, these were stable on the reaction conditions.

Since diazo compounds are toxic, carcinogenic and explosive they are not used on industrial scale and a suitable surrogate is needed especially for the C-H insertion reaction / C-C bond formation. On the other part of the developed work, this objective was meet where the reaction was performed without the usually required diazo compound and metal catalyst also. The dangerous azide precursor for diazo compounds is also replaced by a self stable, commercially available iodine (III) reagent. This method is based on the known phenyliodonium ylide functional group and here the ylide is generated *in situ* at 0 ºC and further decomposed at RT affording β-lactams in up to good yields, skipping one synthetic step and a chromatographic purification. Since the ylide is not isolable, its presence was confirmed by ESI-LRMS^2 experiments. The mechanism investigation revealed a free singlet carbene pathway rather than a radicalar one, since the insertion on chiral C-H bonds proceeds without racemization, affording asymmetric quaternary stereocentes. DFT calculations were again employed and further supported the reaction mechanism. Another characteristic reaction of carbenes, olefin cyclopropanation, was also studied and is feasible. The reaction here discovered deserves further investigation since it offers several advantages.

5. EXPERIMENTAL PART

5.1. General Remarks

5.1.1. General Purification Methods and Reagents

All solvents employed were dried and distilled under argon atmosphere accordingly to standard procedures[126]:

1,2-Dichloroethane:	Distilled over CaH_2
1,2-Dimethoxyethane	Distilled over CaH_2
1,4-Dioxane:	Distilled over Na / benzophenone
Acetonitrile:	Distilled over CaH_2
Dichloromethane:	Distilled over CaH_2
Diethyl Ether:	Distilled over CaH_2 or Na / benzophenone
Methanol:	Distilled over CaH_2
N,N-Dimethylformamide:	Distilled over BaO and under reduced pressure (T < 60 ºC)
n-Hexane:	Distilled over CaH_2
Pentane:	Distilled over CaH_2
Tetrahydrofuran:	Distilled over CaH_2 or Na / benzophenone
Toluene:	Distilled over CaH_2
Triethylamine:	Distilled over CaH_2
Xylenes:	Distilled over CaH_2

Dimethylsulfoxide was bought dried. All the reagents not here described were commercially available and used without further purification. Some α-diazoacetamides were given by Prof. Pedro Góis or Dr. Nuno Candeias. Catalysts $Rh_2(OAc)_4$, $Rh_2(tfa)_4$, Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-MEOX)$_4$ were bought from Sigma-Aldrich. Catalysts $Rh_2(OAc)_4$(IPr), $Rh_2(OAc)_4$(SIPr), $Rh_2(OAc)_4^{Cl}$(IPr) and $Rh_2(cap)_4$ were given by Dr. Alexandre Trindade as well as the carbene salt 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazolinium chloride. Some sulfonium ylides were made in partnership with Prof. Xueliang Huang, others were given, as well as the Echavarren's gold (I) catalyst. Iodosobenzene[127], 1-(diacetoxyiodo)-4-fluorobenzene[128], 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one[129] and 4-Diacetoxyiodoanisole[128] were synthesized and obtained accordingly to published procedures. (Diacetoxyiodo)benzene (DIB) was

bought from Sigma-Aldrich and a colorless solution is obtained in THF. Unless otherwise stated, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one was distilled under reduced pressure and stored at 4 ºC, maintaining the colorless look for more than one year. NaH was used as a dispersion of 60 % in mineral oil. NaO^tBu and KO^tBu was sublimated and stored under Argon. THF-*d8* was bought from Sigma-Aldrich and was dried with activated molecular sieves 4Å and degassed by bubbling Argon.

5.1.2. Detection, Isolation and Purification of Reaction Products

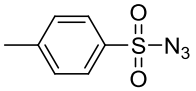
Flash chromatographies were carried out on silica gel Merck (Ref. 109385), Sharlau (230-400 mesh), deactivated alumina from Merck (ref. 1.01097). Reaction mixtures were analyzed by TLC on silica 60 F_{254} from Merck (ref. 1.05554) and aluminium oxide 60 F_{254} from Merck (ref. 105550). Preparative thin layer chromatographies were carried out on silica 60 F_{254} from Merck (ref. 1.07730), basic alumina oxide 60 F_{254} from Merck (ref. 105788) and RP-18 F_{254} from Merck (105434). Silica gel automatic chromatographies were carried on a CombiFlash *Rf* Teledyne ISCO. Visualization of TLC spots was performed by use of UV, phosphomolybdic acid solution or with I_2 dispersed is silica.

5.1.3. Reaction Products Characterization

NMR spectra were recorded with a Bruker Ultrashield Avance II 300, 400 or Bruker Ultrashield Plus Avance III 500 with TMS for ^1H and ^{13}C, $CFCl_3$ for ^{19}F and H_3PO_4 for ^{31}P (external standards). A Bruker Ultrashield Avance II 300 was used for monitoring the reaction evolution at 0 ºC in IST-UL, Lisbon. ^1H NMR splitting patters (J) were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), pentet (p) or septet (sp). All new compounds were characterized with ^1H, ^{13}C (and when justified by ^{19}F or ^{31}P). Bidimensional NMR experiments (COSY, DEPT 135, HSQC, HMQC) were also performed. For the cases where previously described products were obtained, ^1H and ^{31}P NMR (when phosphorous is present) spectra were recorded and compared with original spectra or chemical shifts described in the literature. Melting points were determined on a Electrothermal Mod. IA6304 or Start Mod. SMP10 capillary apparatus without

correction. IR spectra were recorded on FTIR Shimadzu IR Affinity-1 or Jasco FT / IR-430. High- and low-resolution mass spectra (EI and ESI) were carried by the mass spectrometry services from Max-Planck-Institut für Kohlenforschung (Germany) or from the University of Santiago de Compostela (Spain); MS/MS experiments were performed on Micromass Quattro Micro triple quadrupole (Waters, Ireland) with an electrospray (ESI) ion source at Faculty of Pharmacy form UL (Lisbon). Elemental analyses were performed in a Flash 2000 CHNS-O analyzer (ThermoScientific, UK) at Faculty of Pharmacy form UL (Lisbon). X-ray crystallography was carried out by the X-ray crystallography service of the University of Santiago de Compostela (Spain). High Pressure Liquid Chromatography for the enantiomeric excess determination was carried out using a Dionex P680 pump and a diode array detector Dionex UVD3450S.

5.2. Compounds Index



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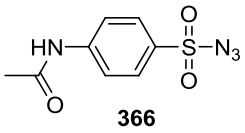

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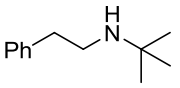

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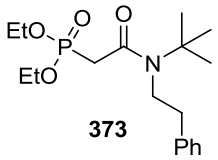

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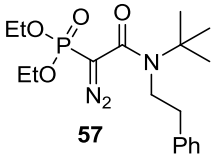

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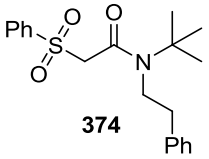

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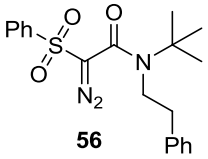

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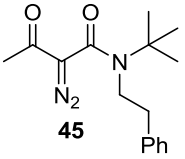

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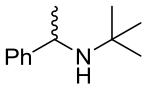

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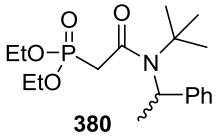

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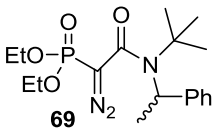

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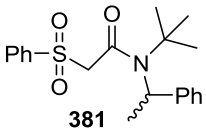

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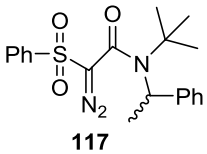

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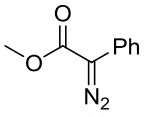

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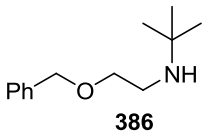

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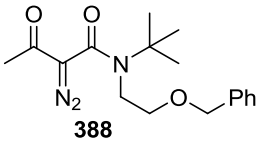

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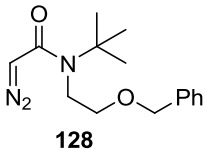

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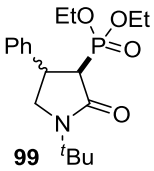

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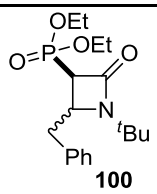

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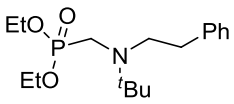

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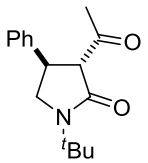

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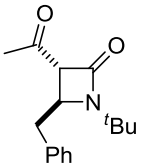

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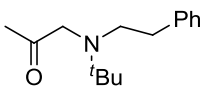

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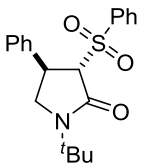

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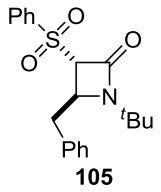
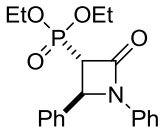
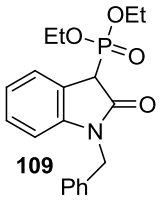
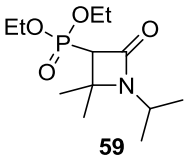
 **105**	 **108**	 **109**	 **59**
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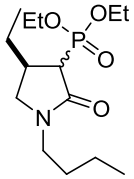
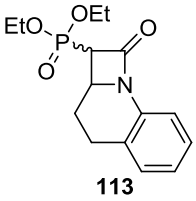
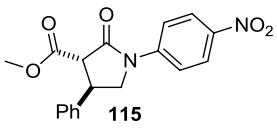
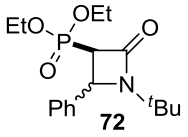
 **111**	 **113**	 **115**	 **72**
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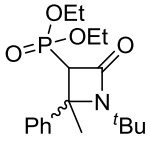
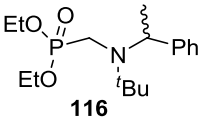
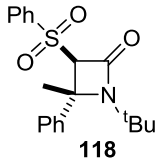
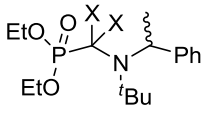
 **70**	 **116**	 **118**	 X=H, D **120**
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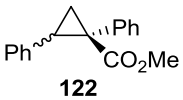
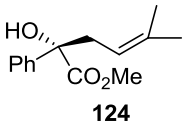
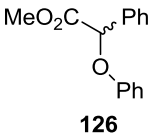
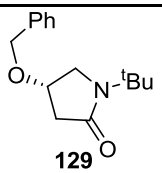
 **122**	 **124**	 **126**	 **129**
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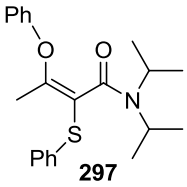
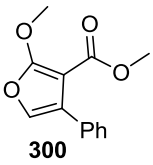
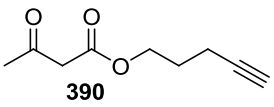
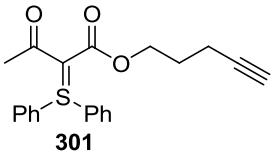
 **297**	 **300**	 **390**	 **301**
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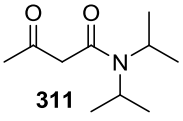
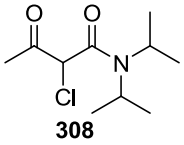
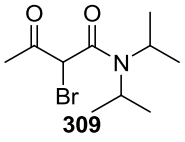
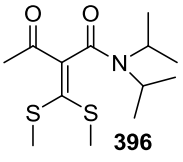
 **311**	 **308**	 **309**	 **396**
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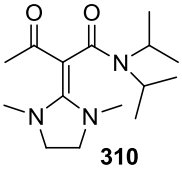
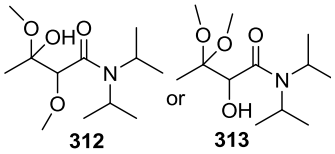
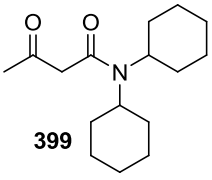
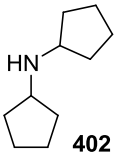
 **310**	 **312** or **313**	 **399**	 **402**
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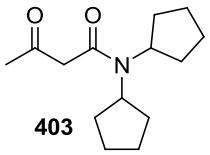	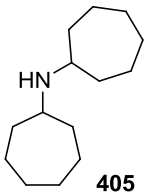	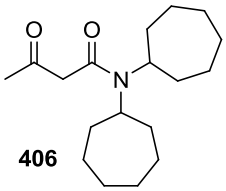	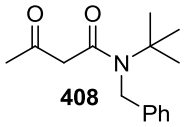
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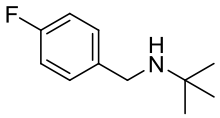	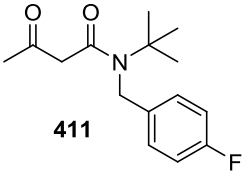	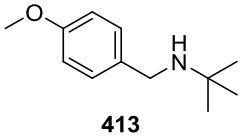	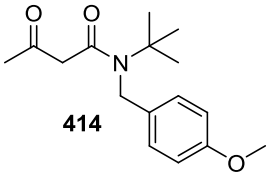
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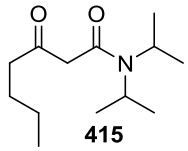	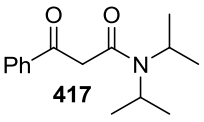	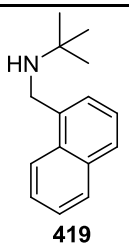	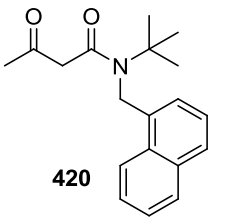
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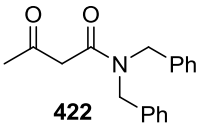	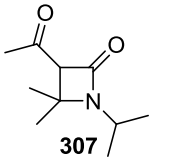	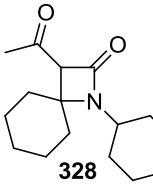	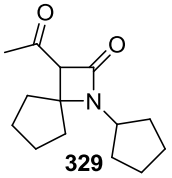
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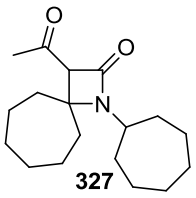	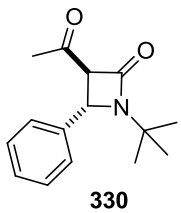	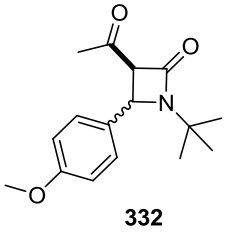	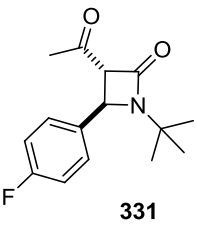
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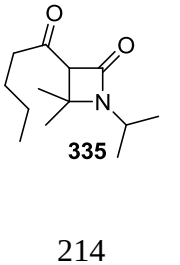	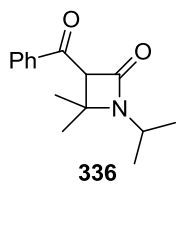	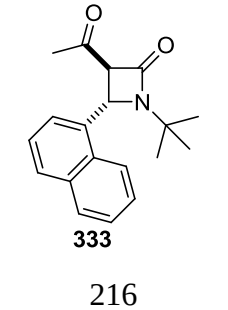	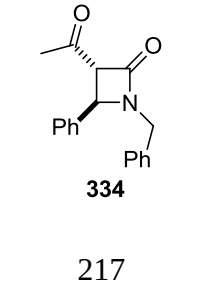
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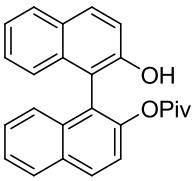

S-**425**

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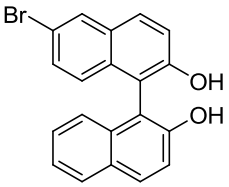

S-**426**

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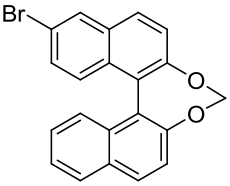

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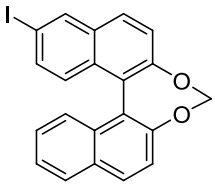

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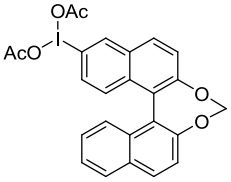

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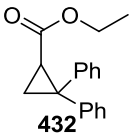

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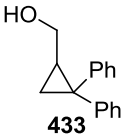

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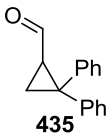

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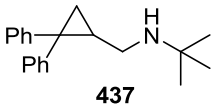

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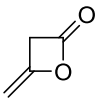

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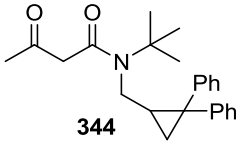

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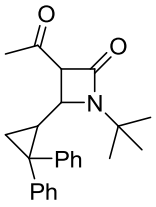

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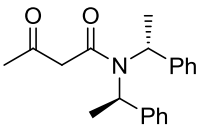

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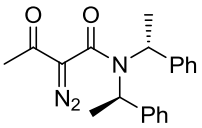

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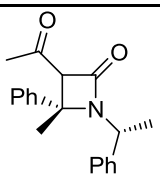

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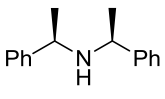

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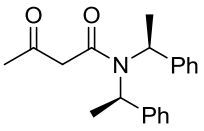

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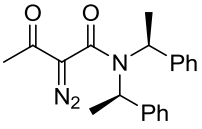

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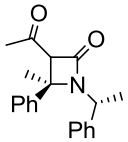

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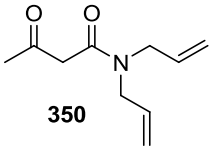

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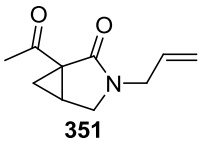

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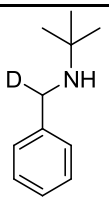

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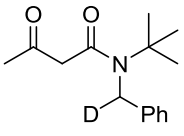

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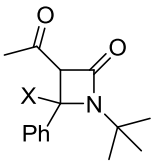

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353" X=H

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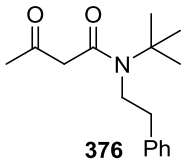
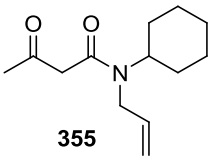
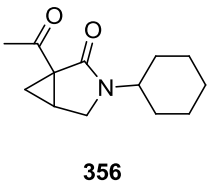
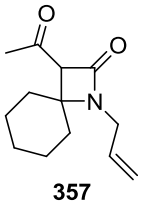
 **376**	 **355**	 **356**	 **357**
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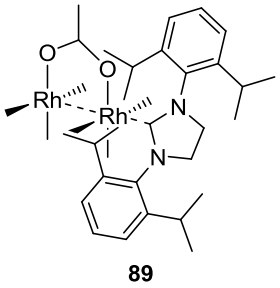
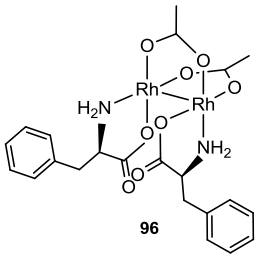
 **89**	 **96**
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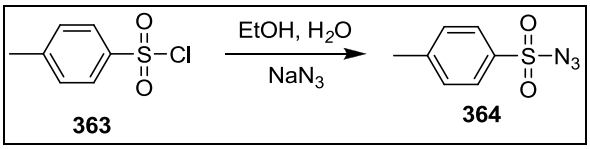
5.4. Preparation of Diazo Transfer Reagents

5.4.1.1. Synthesis of *p*-toluenesulfonyl azide



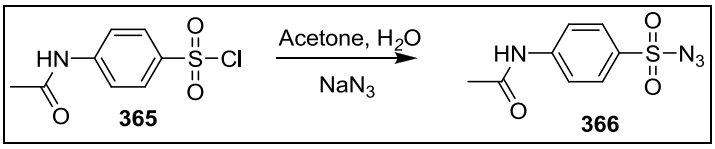
Scheme 170

Compound obtained as previously described[130].

To a solution of *p*-toluenesulfonyl chloride **363** (6.032 g, 31.63 mmol) in stirring ethanol (30 mL), was quickly added a solution of sodium azide (2.457 g, 37.80 mmol) in water (6 mL). After 0.5 h under stirring was added water (120 mL). The solution was stirred for 1 h and the mixture extracted with Et_2O (3 x 90 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure where the *p*-toluenesulfonyl azide **364** (6.032 g, 97%) was obtained as a colorless liquid which solidifies after a night in the fridge.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H, C*H*$_3$Ph), 7.40 (d, J=8.4 Hz, 2H, SCC*H*$_2$), 7.84 (d, J=8.4 Hz, 2H, CH_3CC*H*$_2$).
^{13}C NMR (75 MHz, $CDCl_3$): δ 22.07 (*C*H$_3$C), 127.84, 130.60, 135.80, 146.55 (*Ar*).

5.4.1.2. Synthesis of *p*-acetamidobenzenesulfonyl azide



Scheme 171

Compound obtained as previously described[131].

A solution of sodium azide (3.90 g, 60.0 mmol) in water (30 mL) was quickly added to a solution of *p*-toluenesulfonyl chloride **365** (11.70 g, 50.0 mmol) in acetone

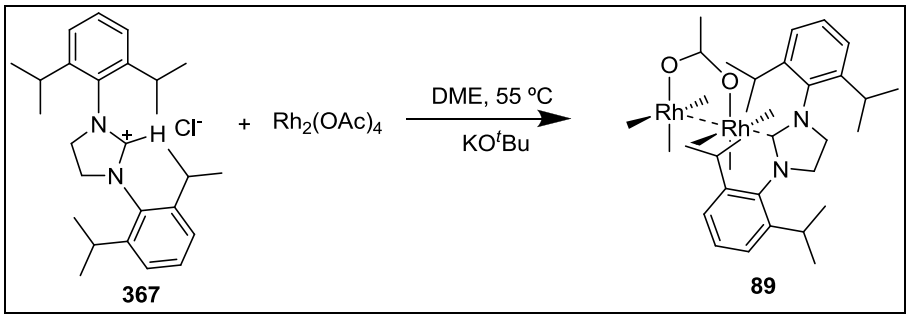
(100 mL). The mixture was stirred at room temperature for 12 h and then water (450 mL) was added. The solution was stirred for 1.5 h. The white precipitate was filtered and recristalized from toluene (650 - 700 mL), where the *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) **366** (9.95 g, 83 %) was obtained as white needles.

^{1}H NMR (300MHz, $CDCl_3$): δ 2.26 (3H, s, CH_3CO), 7.78 (d, J=8.9 Hz, 2H, SCCH_2), 7.92 (d, J=8.4 Hz, 2H, NHCCH_2).

5.5. Dirhodium (II)-Catalyzed α-Diazoacetamides Decomposition

5.5.1. Catalysts Synthesis

5.5.1.1. Synthesis of catalyst $Rh_2(OAc)_4(SIPr)$



367 **89**

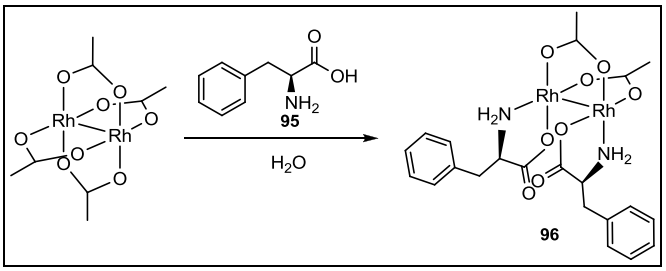
Scheme 172

Compound obtained as previously described[48a].

To a dry shlenk was added 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazolinium chloride **367** (168 mg, 0.40 mmol), sublimated KO^{t}Bu (60 mg, 0.54 mmol) and $Rh_2(OAc)_4$ (60, 0.13 mmol). The reagents were degassed and DME (2 mL) was added. The suspension was stirred at 55º C during 1.5h. The solvent was removed under reduced pressure and the reactional mixture was dissolved in toluene, (2 mL) and successively filtrated *via* canula to another shlenk (3 x 1 mL). The mixture was subjected to preparative TLC (30 % AcOEt in hexanes) where the complex $Rh_2(OAc)_4$(SIPr) **89** (89 mg, 80%) was isolated.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, J= 6.9 Hz, 12 H, ArCH(CH_3)$_2$), 1.39 (d, J= 6.8 Hz, 12H, ArCH(CH_3)$_2$), 1.56 (s, 12H, CH_3COO), 3.64-3.71 (m, 4H, ArC*H*(CH_3)$_2$), 4.25 (s, 4H, NCH_2CH_2N), 7.15-7.27 (m, 6H, Ar).

5.5.1.2. Synthesis of catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$

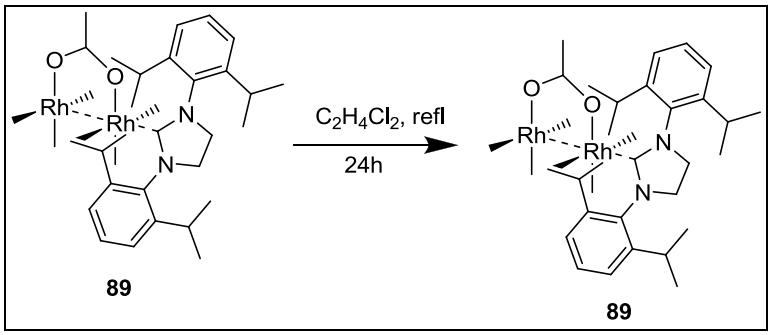


Scheme 173

To a solution of $Rh_2(OAc)_2$ (150 mg, 0.339 mmol) in water (175 mL) was added (*S*)-phenylalanine (281 mg, 1.70mmol). The mixture was heated at 80 ºC for 70 h. Due to the foam formation, the solvent was carefully removed by slow evaporation under reduced pressure (30-35 ºC, 20 mbar, 2 days). The residue was suspended in methanol and purified by reversed phase preparative TLC (RP-18, 30 % EtOH in water). The product was extracted from the RP silica with EtOH and after solvent removal, THF was added and the residue filtrated providing $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** (54.8 mg, 25 %) as a green solid.

^{1}H NMR (400 MHz, D_2O): δ 1.85 (s, 3H, O_2CCH_3); 2.41 (t, J=12.8 Hz, 1H, PhCH_2CHNH_2); 3.24 (d, J=12.6 Hz, 1H, PhCH_2CHNH_2); 3.80 (bs, 1H, PhCH_2C*H*NH_2); 5.14 (bs, 1H, NH_2); 7.27 –7.37 (m, 5H, *Ph*).

5.5.1.3. Stability test of $Rh_2(OAc)_4$(SIPr) with temperature

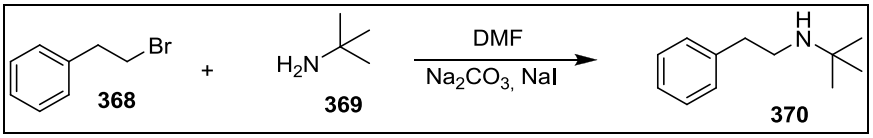


Scheme 174

A solution of $Rh_2(OAc)_4$(SIPr) **89** (10 mg, 12.0 μmol) in 1,2-dichloroethane (5.6 mL) was stirred at reflux for 24h. The solvent was removed at reduced pressure. The ^{1}H NMR spectra was similar to one obtained before this test.

5.5.2. Preparation of Substrates

5.5.2.1. Synthesis of N-(*tert*-butyl)-N-(phenylethyl)amine



Scheme 175

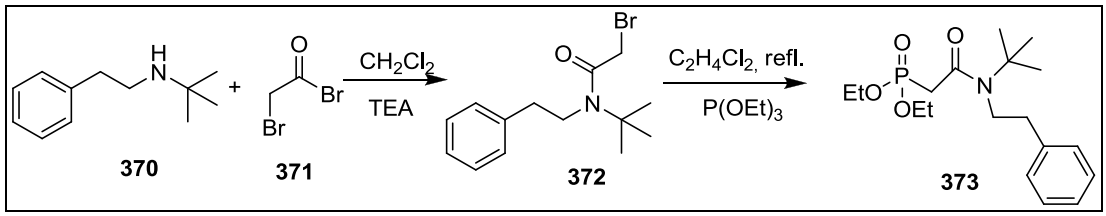
Compound obtained as previously described[39].

To a solution of *tert*-butylamine **369** (7.9 mL, 75.3 mmol), sodium carbonate (5.248 g, 50.0 mmol) and sodium iodide (0.30 g, 2.0 mmol) in DMF (100 mL), was added at RT and during 20 min. a solution of (2-bromoethyl)benzene **368** (6.8 mL, 50.0 mmol) in DMF (20 mL). The mixture was heated under stirring at 65 ºC during 4h and then left stirring overnight at RT. Water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with water (100 mL) followed by brine and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was distilled at reduced pressure. The N-(*tert*-butyl)-

N-(phenylethyl)amine **370** (4.62 g, 52%) was collected at 50 ºC, 0.4 mbar as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H, NC(CH_3)$_3$), 2.76-2.81 (m, 4H, NCH_2CH_2Ph), 7.21-7.32 (m, 5H, NCH_2CH_2*Ph*).
^{13}C NMR (75 MHz, $CDCl_3$): δ 29.11 (NC(*C*H_3)$_3$), 37.37 (NCH_2*C*H_2Ar), 44.22 (N*C*H_2CH_2Ar), 50.32 (N*C*(CH$_3$)$_3$), 126.21, 128.51, 128.77, 140.35 (*Ar*).

5.5.2.2. Synthesis of N-(*tert*-butyl)-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide



Scheme 176

Compound obtained as previously described[41].

To a solution of N-(*tert*-butyl)-N-(phenylethyl)amine **370** (1.50 g, 8.5 mmol), TEA (1.4 mL, 10.1 mmol) in CH_2Cl_2 (16.9 mL) under stirring and at 0 ºC was added dropwise α-bromoacetyl bromide **371** (0.8 mL, 9.3 mmol). The mixture was briefly stirred at 0 ºC and then at RT during 1 h. The mixture was washed with aq. HCl (10 %) and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried with anhydrous sodium sulfate and the solvent was removed at reduced pressure. It was obtained as a brown reactional mixture (2.3 g, 92 %) which was used without further purification.

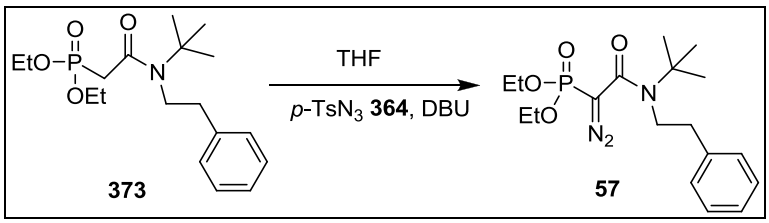
The reactional mixture obtained previously (2.3 g) was dissolved in $C_2H_4Cl_2$ (3.1 ml) and was added triethylphosphite (1.6 mL, 9.2 mmol). The mixture was refluxed under stirring during 4h. The volatile compounds were removed at reduced pressure and the residue purified through silica flash chromatography (50 % AcOEt in hexanes) where N-(*tert*-butyl)-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide **373** (1.49 g, 50 % two steps) was obtained.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25-1.30 (m, 6H, OCH_2CH_3), 1.46 (s, 9H, $NC(CH_3)_3$), 2.78-2.97 (m, 4H, overlapped signals, NCH_2CH_2Ar, $POCH_2CO$), 3.57-3.64 (m, 2H, NCH_2CH_2Ph), 4.05-4.16 (m, 4H, OCH_2CH_3), 7.12-7.25 (m, 5H, *Ph*).

^{13}C NMR (75 MHz, $CDCl_3$): δ 16.35 (OCH_2CH_3), 28.92 ($NC(CH_3)_3$), 36.02 (d, J_{C-P} 132.8, $POCH_2CO$), 38.12 (NCH_2CH_2Ph), 47.61 (NCH_2CH_2Ph), 57.81 ($NC(CH_3)_3$), 62.33 (OCH_2CH_3), 126.74, 128.45, 128.78, 138.01 (*Ph*), 165.36 (*C*=O).

^{31}P NMR (120 MHz, $CDCl_3$): δ 21.92.

5.5.2.3. Synthesis of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide



Scheme 177

Compound obtained as previously described[41].

To a solution of N-(*tert*-butyl)-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide **373** (1.49 g, 4.4 mmol) and *p*-TsN_3 **364** (1.02 g, 5.1 mmol) in THF (21.5 mL) under stirring was added DBU (0.7 mL, 4.6 mmol) at RT. After 24 h the mixture was concentrated at reduced pressure and water (17 mL) was added followed by Et_2O (17 mL). The aqueous phase was extracted with Et_2O (3 x 17 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and the solvent removed. The residue was purified through silica flash chromatography (40 % AcOEt in hexanes) where N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide **57** (1.0 g, 59 %) was obtained as a yellow oil.

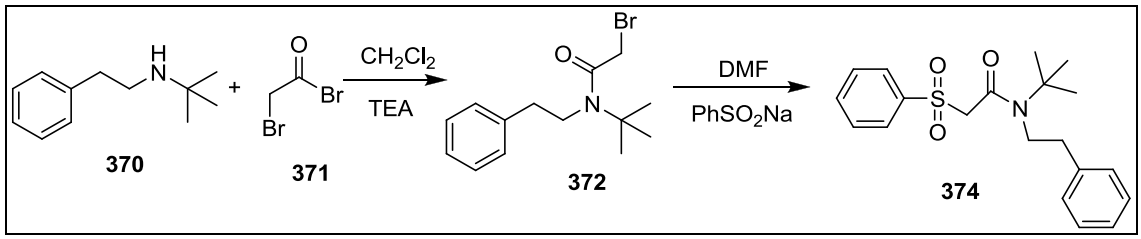
R_f = 0.45 (silica, 40 % AcOEt in hexanes)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 6H, OCH_2CH_3), 1.48 (s, 9H, $NC(CH_3)_3$), 2.89 (t, J=7.6 Hz, 2H, NCH_2CH_2Ph), 3.67 (t, J=7.6 Hz, 2H, NCH_2CH_2Ph), 4.10-4.23 (m, 4H, OCH_2CH_3), 7.20-7.33 (m, 5H, *Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.38, 16.45 ($OCH_2\mathit{C}H_3$), 29.39 ($NC(\mathit{C}H_3)_3$), 38.54 ($NCH_2\mathit{C}H_2Ph$), 48.98 ($N\mathit{C}H_2CH_2Ph$), 58.29 ($N\mathit{C}(CH_3)_3$), 63.63, 63.68 ($O\mathit{C}H_2CH_3$), 127.00, 128.94, 128.98, 138.61 (*Ph*), 164.24 (*C*=O).

^{31}P NMR (160 MHz, $CDCl_3$): δ 13.08

5.5.2.4. Synthesis of N-(*tert*-butyl)-2-(phenylsulfonyl)-N-(phenylethyl)acetamide



Scheme 178

Compound obtained as previously described[42].

To a solution of N-(*tert*-butyl)-N-(phenylethyl)amine **370** (1.51 g, 8.5 mmol), TEA (1.4 mL, 10.1 mmol) in CH_2Cl_2 (16.9 mL) under stirring and at 0 ºC was added α-bromoacetyl bromide **371** (0.8 mL, 9.3 mmol) dropwise. The mixture was briefly stirred at 0 ºC and then at RT during 1 h. The mixture was washed with aq. HCl (10 %) and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried with anhydrous sodium sulfate and the solvent was removed at reduced pressure. It was obtained as a brown reactional mixture (2.3 g, 92 %) which was used without further purification.

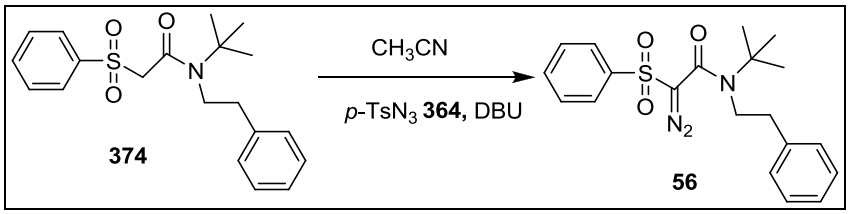
To the reactional mixture obtained previously (2.3 g) in DMF (42.7 mL) was added benzenesulfinic acid sodium salt (1.54 g, 9.4 mmol). The mixture was stirred at RT for 1 h and AcOEt was added. The mixture was washed with water (3x), brine, dried with anhydrous sodium sulfate and the solvent evaporated. The residue was purified through silica flash chromatography (15 % AcOEt in hexanes) where N-(*tert*-butyl)-2-(phenylsulfonyl)-N-(phenylethyl)acetamide **374** (1.05, 34 %) was isolated as a white solid.

R_f = 0.53 (silica, 20 % AcOEt in hexanes)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 9H, NC(CH_3)$_3$), 2.86 (t, J=7.8 Hz, 2H, NCH_2CH_2Ar), 3.73 (t, J= 8.1Hz, 2H, NCH_2CH_2Ar), 3.99 (s, 2H, SCH_2CO), 7.18-7.36 (m, 5H, *Ph*), 7.52-7.68 (m, 3H, *Ph*), 7.87-7.90 (m, 2H, *Ph*).

^{13}C NMR (75 MHz, $CDCl_3$): δ 28.53 (NC(CH_3)$_3$), 38.43 (NCH_2CH_2Ar), 47.88 (NCH_2CH_2Ar), 58.74 (NC(CH_3)$_3$), 62.34 (SCH_2CO), 127.34, 128.88, 129.22, 129.32, 134.30, 138.00, 139.18 (*Ph*), 162.15 (*C*=O).

5.5.2.5. Synthesis of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide



Scheme 179

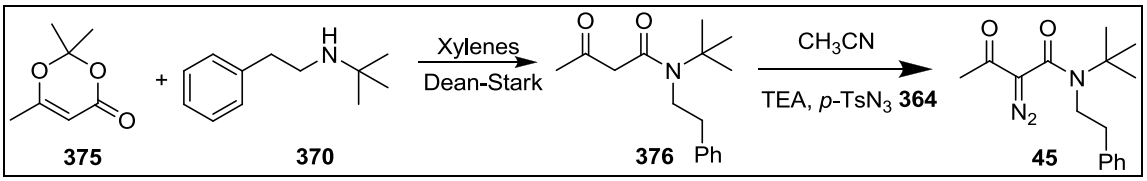
Compound obtained as previously described[42].

To a mixture of N-(*tert*-butyl)-2-(phenylsulfonyl)-N-(phenylethyl)acetamide **374** (1.05 g, 2.92 mmol) and *p*-TsN_3 **364** (0.757 g, 3.84 mmol) in CH_3CN (14.6 mL) was slowly added DBU (0.48 mL, 3.20 mmol) at RT. The solution was stirred for 0.5 h and the solvent evaporated. The residue was diluted with Et_2O and successively washed with aqueous NaOH (1 M), water and brine. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica flash chromatography (25 % AcOEt in hexanes) where N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide **56** (0.580, 52 %) was obtained as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H, NC(CH_3)$_3$), 2.85 (t, J=7.8 Hz, 2H, NCH_2CH_2Ph), 3.72 (t, J= 7.2 Hz, 2H, , NCH_2CH_2Ph), 7.17-7.35 (m, 5H, *Ph*), 7.51-7.65 (m, 3H, *Ph*), 7.93-7.96 (m, 2H, *Ph*).

^{13}C NMR (75 MHz, $CDCl_3$): δ 29.01 ($NC(CH_3)_3$), 38.47 (NCH_2CH_2Ph), 49.42 (NCH_2CH_2Ph), 58.62 ($NC(CH_3)_3$), 127.12, 127.76, 129.06, 129.46, 134.00, 138.10, 142.33(*Ph*), 160.09 (*C*=O).

5.5.2.6. Synthesis of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide



Scheme 180

Compound obtained as previously described[132].

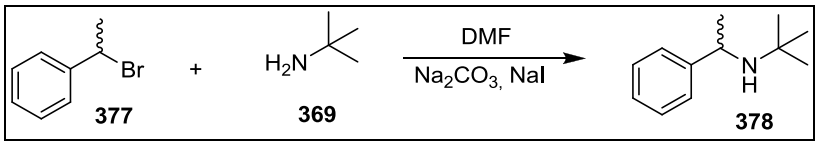
A solution of 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one **375** (at 90% purity, 0.8 mL, 6.01 mmol) and N-(*tert*-butyl)-N-(phenylethyl)amine **370** (1.064 g, 6.01 mmol) in xylenes was heated at 120 ºC during 5 h while removing acetone with a Dean-Stark. Then the mixture was heated at 150 ºC for 0.5 h and the xylenes were evaporated at 120 ºC, 80 mbar. The reaction mixture was used on the next step without further purification.

The reactional mixture was dissolved in dry CH_3CN (12 mL), TEA (1.7 mL, 12.02 mmol) was added and *p*-TsN_3 **364** (1.302 g, 6.60 mmol). The solution was stirred for 15 h at RT and the solvent evaporated under reduced pressure. The residue was purified through silica flash chromatography (20 % AcOEt in hexanes) where N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide **45** (0.895 g, 52 %) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 9H, $NC(CH_3)_3$), 2.16 (s, 3H, CH_3CO) 2.87 (t, J=7.2 Hz, 2H, NCH_2CH_2Ph), 3.62 (t, J= 7.2 Hz, 2H, NCH_2CH_2Ph), 7.14-7.34 (m, 5H, *Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.73 (CH_3CO), 29.09 ($NC(CH_3)_3$), 38.20 (NCH_2CH_2Ph), 49.13 (NCH_2CH_2Ph), 58.11 ($NC(CH_3)_3$), 126.92, 128.77, 128.08, 138.02 (*Ph*), 163.42 (*C*=O).

5.5.2.7. Synthesis of N-(*tert*-butyl)-N-(2-phenylethyl)acetamide



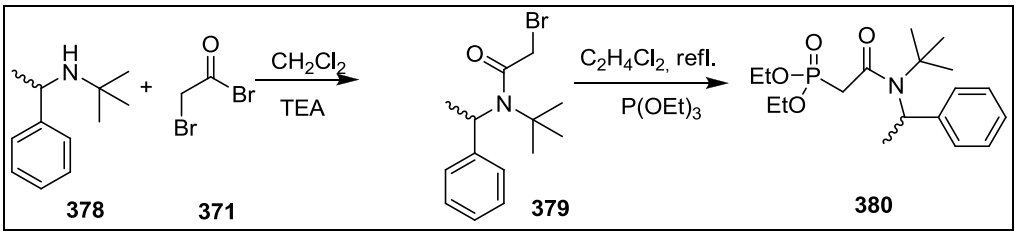
Scheme 181

Compound obtained as previously described[41].

To a solution of *tert*-butylamine **369** (5.0 mL, 47.6 mmol), sodium carbonate (2.317 g, 21.9 mmol) and sodium iodide (0.273 g, 1.2 mmol) in DMF (44 mL), was added at RT and during 20 min. a solution of (1-bromoethyl)benzene **377** (3.0 mL, 22.0 mmol) in DMF (8.7 mL). The mixture was heated under stirring at 65 ºC during 4h and then left stirring overnight at RT. Water (45 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 45 mL). The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was distilled at reduced pressure. The N-(*tert*-butyl)-N-(2-phenylethyl)amine **378** (1.972 g, 51%) was collected at 40 ºC, 0.5 mbar as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 9H, NC(CH_3)$_3$), 1.34 (d, J= 6.6 Hz, 3H, CH_3CHPh), 1.52 (d, J=6.6 Hz; 1H, CH_3CHPh), 7.18-7.33 (m, 5H, CH_3CHPh).
^{13}C NMR (75 MHz, $CDCl_3$): δ 25.22 (NCH(CH_3)Ph), 30.01 (NC(CH_3)$_3$), 52.47 (NCH(CH_3)Ph), 126.31, 127.46, 128.22, 145.90, (*Ph*).

5.5.2.8. Synthesis of N-(*tert*-butyl)-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide



Scheme 182

Compound obtained as previously described[41].

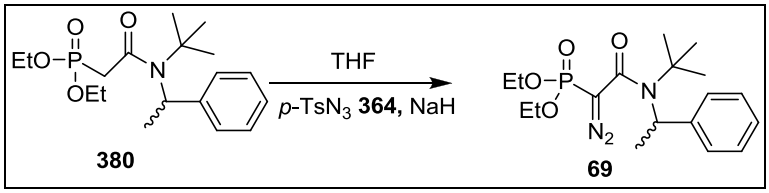
To a solution of N-(*tert*-butyl)-N-(2-phenylethyl)amine **378** (1.970 g, 11.1 mmol), TEA (1.9 mL, 13.6 mmol) in CH_2Cl_2 (25 mL) under stirring and at 0 ºC was added dropwise α-bromoacetyl bromide **371** (0.9 mL, 10.4 mmol). The mixture was briefly stirred at 0 ºC and then at RT during 1 h. The mixture was washed with aq. HCl (5 %) and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried with anhydrous sodium sulfate and the solvent was removed at reduced pressure. It was obtained as a dark- brown reactional mixture (2.351 g, 71 %) which was used without further purification.

The reactional mixture obtained previously (2.351 g) was dissolved in $C_2H_4Cl_2$ (3.2 ml) and was added triethylphosphite (1.6 mL, 9.2 mmol). The mixture was refluxed under stirring during 18 h. The volatile compounds were removed at reduced pressure and the residue purified through silica flash chromatography (40 % AcOEt in hexanes) providing N-(*tert*-butyl)-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **380** (1.105 g, 40 % two steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (q, J=5.7 Hz, 6H, OCH_2CH_3), 1.59 (s, 9H, $NC(CH_3)_3$), 1.82 (d, J=7.2 Hz, 3H, $NCH(CH_3)Ph$), 4.02-4.22 (m, 4H, OCH_2CH_3), 5.15 (q, J=7.21 Hz, H, $NCH(CH_3)Ph$), 7.23-7.40 (m, 5H, *Ph*).

^{31}P NMR (120 MHz, $CDCl_3$): δ 22.40.

5.5.2.9. Synthesis of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide



Scheme 183

Compound obtained as previously described[41].

To a solution of N-(*tert*-butyl)-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **380** (0.831g, 2.3 mmol) and *p*-TsN_3 **364** (0.565g, 2.87 mmol) in THF (15.2 mL) under stirring was added NaH (0.124 mg, 2.81 mmol) at 0ºC. After 1 h under stirring at 0 ºC the reaction was stirred at RT for further 2 h. Water (13 mL) was added followed by Et_2O (13 mL). The aqueous phase was extracted with Et_2O (3 x 13 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and the solvent removed. The residue was purified through silica flash chromatography (30 % AcOEt in hexanes) providing N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (0.747 g, 84 %) as a yellow oil.

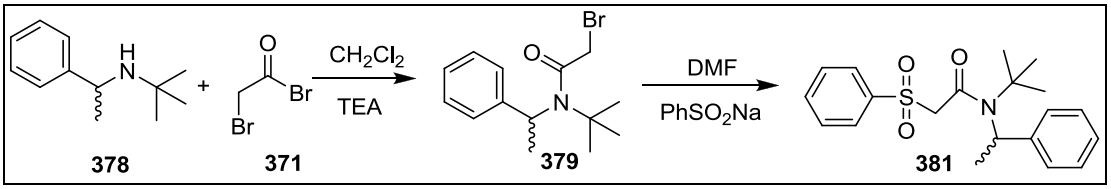
R_f = 0.35 (silica, 30 % AcOEt in hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (q, J=7.2 Hz, 6H, OCH_2CH_3), 1.37 (s, 9H, $NC(CH_3)_3$), 1.83 (d, J=7.2 Hz, 3H, $NCH(CH_3)Ph$), 4.07-4.23 (m, 4H, OCH_2CH_3), 5.17 (q, J=7.2 Hz, 1H, $NCH(CH_3)Ph$), 7.24-7.40 (m, 5H, *Ph*).

^{13}C NMR (75 MHz, $CDCl_3$): δ 16.19, 16.29 (OCH_2CH_3), 20.30 ($NCH(CH_3)Ph$), 29.58 ($NC(CH_3)_3$), 56.29 ($NCH(CH_3)Ph$), 59.72 ($NC(CH_3)_3$), 63.54, 63.50 (OCH_2CH_3), 126.52, 127.25, 128.41, 142.06 (*Ph*), 166.76 (*C*=O).

^{31}P NMR (120 MHz, $CDCl_3$): δ 13.87.

5.5.2.10. Synthesis of N-(*tert*-butyl)-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide



Scheme 184

To a solution of N-(*tert*-butyl)-N-(2-phenylethyl)amine **378** (0.694 g, 3.92 mmol), TEA (0.7 mL, 5.0 mmol) in CH_2Cl_2 (7.8 mL) under stirring and at 0 ºC was added dropwise α-bromoacetyl bromide **371** (0.4 mL, 4.6 mmol). The mixture was briefly stirred at 0 ºC and then at RT during 1 h. The mixture was washed with aq. HCl (10 %) and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried with anhydrous

sodium sulfate and the solvent was removed under reduced pressure. The reactional mixture was used without further purification.

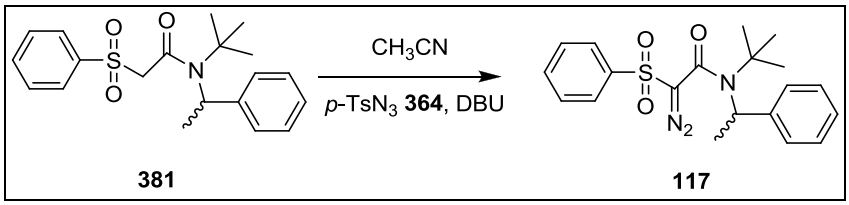
To the reactional mixture obtained previously in DMF (20 mL) was added benzenesulfinic acid sodium salt (0.706 g, 4.3 mmol). The mixture was stirred at RT for 2 h and AcOEt was added. The mixture was washed with water (3x), brine, dried with anhydrous sodium sulfate and the solvent evaporated. The residue was purified through silica flash chromatography (25 % AcOEt in hexanes) where N-(*tert*-butyl)-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide **381** (0.739 g, 53 %) was isolated as a white solid.

R_f = 0.36 (silica, 30 % AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 9H, NC(CH_3)$_3$), 1.85 (d, J= 6.8 Hz, 3H, CH_3CHN), 3.59 (d, J=14.4 Hz, 1H, SO_2*H*HCO), 3.90(d, J=14.8 Hz, 1H, SO_2H*H*CO), 5.12 (q, J=6.8 Hz, 1H, CH_3C*H*N), 7.29-7.32 (m, 3H, *Ph*), 7.38-7.41 (m, 2H, *Ph*), 7.50-7.54 (m, 2H, *Ph*), 7.61-7.65 (m, 1H, *Ph*), 7.81-7.83 (m, 2H, *Ph*).

^{13}C NMR (100MHz, $CDCl_3$): 21.32 (CH_3CHPh), 29.04 (NC(CH_3)$_3$), 52.66 (CH_3CHPh), 59.87 (NC(CH_3)$_3$), 63.38 (SO_2CH_2CO), 125,57, 127.20, 128.72, 128.81, 129.26, 133.57, 139.92, 142.87 (*Ph*), 164.01 (*C*=O).

5.5.2.11. Synthesis of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide



Scheme 185

To a mixture of N-(*tert*-butyl)-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide **381** (0.516 g, 1.44 mmol) and *p*-TsN_3 **364** (0.317 g, 1.61 mmol) in CH_3CN (7.2 mL) was slowly added DBU (0.24 mL, 1.60 mmol) at 0 ºC. The solution was stirred for 3 h at RT and the solvent evaporated. The residue was diluted with Et_2O and successively washed with aqueous NaOH (1 M), water and brine. The organic layer was dried with anhydrous sodium sulfate and concentrated. The residue was purified through silica

flash chromatography (7 % AcOEt in hexanes) where N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide **117** (0.331 g, 60 %) was obtained as a yellow solid.

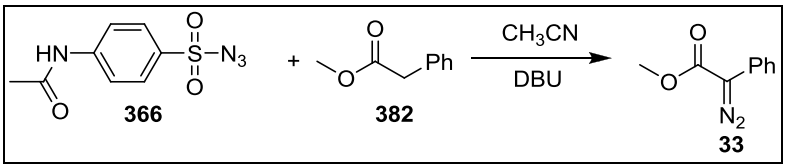
R_f = 0.79 (silica, 30 % AcOEt in hexanes).

IR (neat, cm^{-1}): = 2976, 2091, 1643, 1333, 729

^{1}H NMR (400 MHz, $CDCl_3$): 1.40 (s, 9H, NC(CH_3)$_3$), 1.86 (d, J= 7.2 Hz, 3H, CH_3CHN), 5.11 (q, J=7.2 Hz, 1H, CH_3CHN), 7.30-7.33 (m, 1H, *Ph*), 7.37-7.40 (m, 4H, *Ph*), 7.54-7.58 (m, 2H, *Ph*), 7.62-7.66 (m, 1H, *Ph*), 7.99-8.01 (m, 2H, *Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): 20.13 (CH_3CHPh), 29.22 (NC(CH_3)$_3$), 55.56 (CH_3CHPh), 59.80 (NC(CH_3)$_3$), 126.90, 127.44, 127.90, 128.64, 128.97, 133.48, 141.60, 142.36 (*Ph*), 162.37 (CO).

5.5.2.12. Synthesis of methyl phenyldiazoacetate



Scheme 186

Compound obtained as previously described[133].

To a solution of *p*-ABSA **366** (3.744 g, 15.6 mmol) and methyl phenylacetate **382** (1.9 mL, 13.0 mmol) in CH_3CN (45.5 mL) at 0 ºC was added DBU (2.3 mL, 15.6 mmol) under stirring. The mixture was stirred at RT for 4h. A saturated aqueous solution of NH_4Cl was added and extracted with Et_2O (3x). The combined organic layers were dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The solid residue was triturated and washed with Et_2O/ Hexanes (1:1). The solid was removed by filtration and the solvent removed under reduced pressure. The residue was purified through silica flash chromatography (3 % AcOEt in hexanes). To remove the AcOEt, hexanes were added and the solvents evaporated (3x). Methyl phenyldiazoacetate **33** (1.398 g, 61 %) was obtained as an orange liquid.

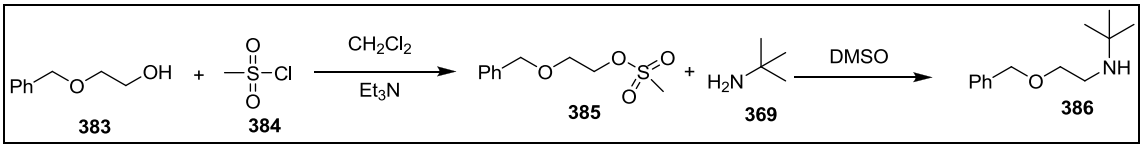
Volatile liquid.

R_f = 0.51 (silica, 10 % AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.883 (s, 3H, C*H*$_3$O), 7.18-7.42 (m, 5H, *Ph*).

^{13}C NMR (75 MHz, $CDCl_3$): δ 51.96 (*C*H$_3$O), 123.94, 125.46, 125.82, 128.93 (*Ph*), 165.56 (*C*=O).

5.5.2.13. Synthesis of 2-benzyloxyethyl-*tert*-butyl-amine



Scheme 187

Compound obtained as previously described[61].

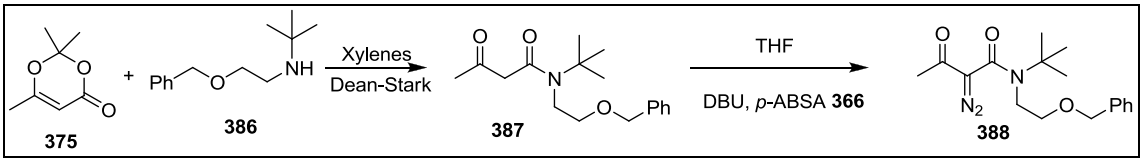
To a solution of benzyloxyethyl alcohol **383** (1.4 mL, 9.86 mmol) in CH_2Cl_2 (25 mL) at 0º C was added TEA (1.7 mL, 11.82 mmol) and methanesulfonyl chloride **384** (1 mL, 12.8 mmol). After 3h at RT water/ice (10 mL) was added and the organic layer was washed with saturated aqueous NaHCO3 and brine and was dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude was used on the next step without further purification.

The crude obtained previously was dissolved in DMSO (10 mL) and *tert*-butylamine **369** (3 mL, 28.4 mmol). The solution was stirred at 50º C for 71 h. It was purged with aqueous KOH (1%) and extracted with AcOEt (2 x 15 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and the solvent removed under reduced pressure. The reaction mixture was distilled at reduced pressure where 2-benzyloxyethyl-*tert*-butyl-amine **386** (0.3 mbar, 81 ºC; 1.924 g, 94 % two steps) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (s, 9H, NC(C*H*$_3$)$_3$), 2.79 (t, J= 5.2 Hz, 2H, NC*H*$_2$), 3.63 (t, J= 5.2 Hz, 2H, OC*H*$_2$), 4.55 (s, 2H, C*H*$_2$Ph), 7.27-7.33 (m, 5H, *Ph*).

^{13}C NMR (100MHz, $CDCl_3$): δ 29.02 (NC(*C*H$_3$)$_3$), 42.22 (N*C*H$_2$), 50.00 (N*C*(CH$_3$)$_3$),70.67(O*C*H$_2$), 73.11(*C*H$_2$Ph), 127.59, 127.74, 128.18, 128.38, 138.41 (*Ph*).

5.5.2.14. **Synthesis of 2-acetyl-N-(2-benzyloxyethyl)-N-*tert*-butyl-2-diazoacetamide**



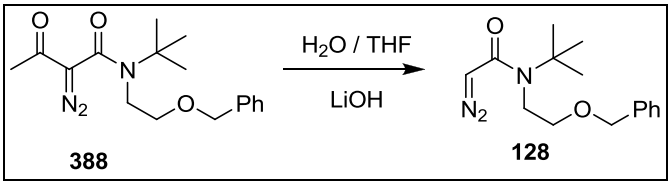
Scheme 188

Compound obtained as previously described[61].

A solution of 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one **375** (346 mg, 2.44 mmol) and 2-benzyloxyethyl-*tert*-butyl-amine **386** (505 mg, 2.44 mmol) in xylenes (0.5mL) was heated at 120 ºC during 5 h while removing acetone with a Dean-Stark. Then the mixture was heated at 150 ºC for 0.5 h and the xylenes were evaporated at 120 ºC, 80 mbar. The reaction mixture was used on the next step without further purification.

The previous reaction mixture was dissolved in THF (5.6 mL) and was added *p*-ABSA **366** (676.8 mg, 2.8 mmol) followed by DBU (418 μL, 2.8 mmol) at RT. The solution was stirred for 17 h. NH_4Cl aq. sat. was added and the solution was extracted with Et_2O (3x). The combined organic layers were dried with anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified through silica flash chromatography (20 % AcOEt in hexanes) providing 2-acetyl-N-(2-benzyloxyethyl)-N-*tert*-butyl-2-diazoacetamide **388** (0.428 g, 55 % two steps).

5.5.2.15. **Synthesis of N-(2-Benzyloxyethyl)-N-*tert*-butyl-2-diazocetamide**



Scheme 189

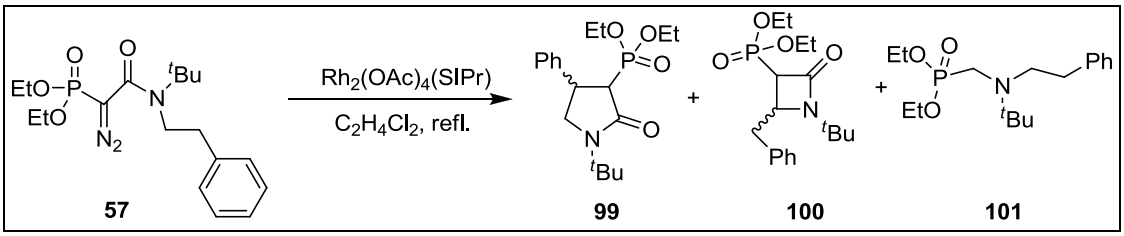
Compound obtained as previously described[61].

To a 2-acetyl-N-(2-benzyloxyethyl)-N-*tert*-butyl-2-diazoacetamide **388** (428 mg, 1.35 mmol) in THF (5.6 mL) and water (9.4 mL) was added LiOH (217 mg, 9.04 mmol) at RT. The solution was stirred for 17 h. AcOEt was added and and the organic phase was washed with water and dried with anhydrous magnesium sulfate. The solvent was removed and the reaction mixture was purified through neutral alumina flash chromatography (5% AcOEt in hexanes) providing N-(2-enzyloxyethyl)-N-*tert*-butyl-2-diazocetamide[61] **128** (233 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, NC(CH_3)$_3$), 3.37 (t, J= 6.0 Hz, 2H), 3.54 (t, J= 6.4 Hz, 2H), 4.55 (s, 2H PhCH_2), 5.19 (s, 1H, *H*CN_2), 7.29-7.39 (m, 5H, *Ph*).

5.5.3. Rh (II)-Catalyzed Reactions with Diazo Compounds

5.5.3.1. Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4$(SIPr)



Scheme 190

A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide **57** (119.0 mg, 0.312 mmol) in $C_2H_4Cl_2$ (3.5 mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (2.8 mg, 3.36×10^{-3} mmol). The mixture was stirred under reflux for 24 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina preperative TLC (40 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-γ-lactam[41] **99** (75.6 mg, 66 %), *trans*-4-benzyl-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-β-lactam **100** (7.8 mg, 7 %) and N-(*tert*-butyl)-N-phenyl-(methyl-diethoxyphosphoryl)-amine **101** (9.2 mg, 9%).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **99** (79%) (*cis/trans*: 0.06/1), **100** (8%) (*cis/trans*: 2.6/1), **101** (9%).

trans-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-γ-lactam **99**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.28 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.43 (s, 9H, $NC(CH_3)_3$), 2.99 (dd, J_{P-H}= 22.3 Hz, J= 4.9 Hz, 1H, POC*H*CO), 3.43 (dd, J=2.5 Hz, J=9.8 Hz, 1H, $CHPhCH_2N$), 3.66-3.79 (m, 1H, $CHArCH_2N$), 3.95-3.99 (m, 1H, $CHPhCH_2N$), 4.02-4.21 (m, 4H, OCH_2CH_3), 7.22-7.32 (m, 5H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 16.52, 16.64 (OCH_2CH_3), 27.83 ($NC(CH_3)_3$), 38.52 ($CHArCH_2N$), 52.38 (d, J_{C-P}= 138.13 Hz, POCHCO), 53.37 ($CHPhCH_2N$), 54.99 ($NC(CH_3)_3$), 62.50, 63.19 (OCH_2CH_3), 126.79, 127.56, 128.97, 143.76 (*Ph*); 169.01 (*C*=O).
^{31}P NMR (160 MHz, $CDCl_3$): δ 23.26.

trans-4-benzyl-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-β-lactam **100** (from a mixture of with **99**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, J= 7.2 Hz, 3H, OCH_2CH_3), 1.18 (t, J= 7.2 Hz, 3H, OCH_2CH_3), 1.427, (s, overlapped signals, 9H, $NC(CH_3)_3$), 2.66 (dd, J= 13.6 Hz, J= 9.6 Hz, 1H, PhCHHCH), 3.09 (dd, J_{P-H}= 15.2 Hz, J= 2.0 Hz, 1H, COCHP), 3.37(ddd, J= 13.6 Hz, J= 4.0 Hz, J= 2.0 Hz, 1H, CH_2CHN), 3.67-3.83 (m, 1H, overlapped signals, PhCHHCH), 3.96-4.11 (m, 4H, overlapped signals, OCH_2CH_3), 7.17-7.33 (m, 5H, overlapped signals, *Ph*).
^{31}P NMR (160 MHz, $CDCl_3$): δ 20.05.

N-(*tert*-butyl)-N-phenyl-(methyl-diethoxyphosphoryl)-amine **101**:

R_f = 0.63 (neutral alumina, 30 % AcOEt in hexanes).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (s, 9H, $NC(CH_3)_3$), 1.36 (t, J= 7.0 Hz, 6H, OCH_2CH_3), 2.89 (s, 4H, NCH_2CH_2Ph), 3.03 (d, J_{P-H}= 10.92 Hz, 1H, PCH_2N), 4.16-4.23 (m, 4H, OCH_2CH_3), 7.16-7.30 (m, 5H, *Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.51, 16.56 (OCH_2CH_3), 27.14 ($NC(CH_3)_3$), 37.54 ($PhCH_2CH_2N$), 47.00 (d, J_{P-C}=170.0 Hz, PCH_2N), 54.65 ($PhCH_2CH_2N$), 55.85 ($NC(CH_3)_3$), 61.93, 62.00 (OCH_2CH_3), 125.81, 128.28, 128.81, 140.78 (*Ph*).

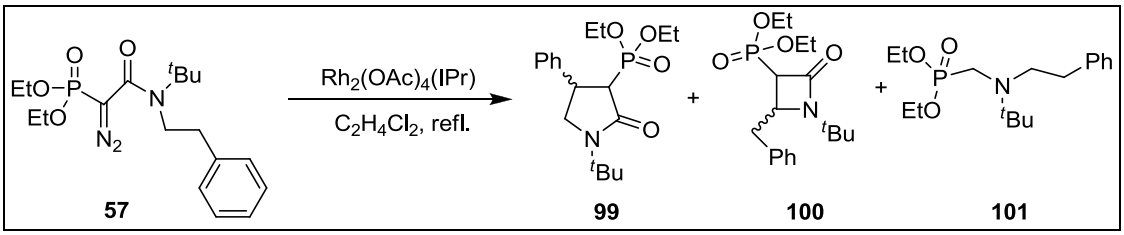
^{31}P NMR (160 MHz, $CDCl_3$): δ 26.84.

IR (neat, cm^{-1}): 2974 (C-H), 1261 (P-O), 1057, 1030 (P=O), 960.

MS (FAB^+) *m/z*: 328, 236, 190, 134.

HMRS (FAB^+): *m/z* calcd. $[M+H]^+$= 328.204158, found $[M+H]^+$: 328.205358.

5.5.3.2. Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4(IPr)$

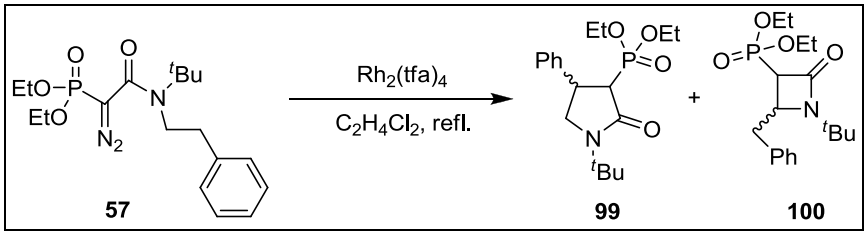


Scheme 191

A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide **57** (115.6 mg, 0.303 mmol) in $C_2H_4Cl_2$ (3.5 mL) was added to the catalyst $Rh_2(OAc)_4(IPr)$ (2.5 mg, 3.00×10^{-3} mmol). The mixture was stirred under reflux for 46 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-γ-lactam[41] **99** (59.6mg, 56 %), *trans*-4-benzyl-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-β-lactam **100** (7.4 mg, 7 %) and N-(*tert*-butyl)-N-phenyl-(methyl-diethoxyphosphoryl)-amine **101** (25.6 mg, 23 %).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **99** (60%) (*cis/trans*: 0.07/1), **100** (9%) (*cis/trans*: 2.7/1), **101** (25%).

5.5.3.3. Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide with $Rh_2(tfa)_4$

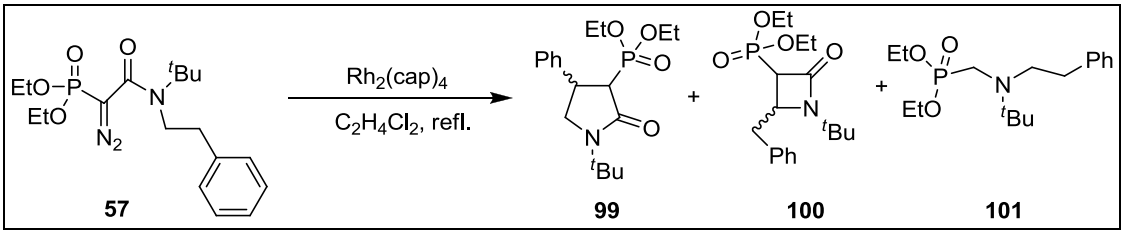


Scheme 192

A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide **57** (60.0 mg, 0.157 mmol) in $C_2H_4Cl_2$ (1.8 mL) was added to the catalyst $Rh_2(tfa)_4$ (1mg, 1.52×10^{-3} mmol). The mixture was stirred under reflux for 12 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-γ-lactam[41] **99** (41.6 mg, 66 %) and *trans*-4-benzyl-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-β-lactam **100** (6.0 mg, 10 %).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **99** (82%) (*cis/trans*: 0.02/1), **100** (11%) (*cis/trans*: 3.9/1).

5.5.3.4. Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide with $Rh_2(cap)_4$



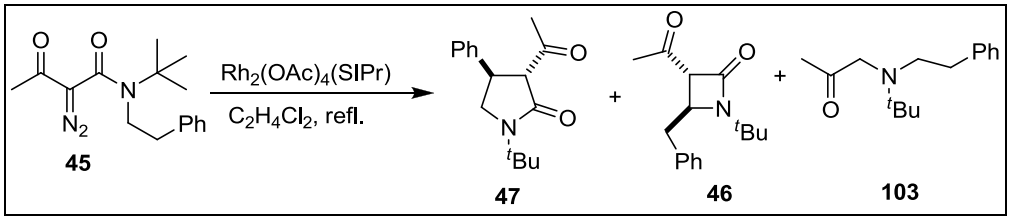
Scheme 193

A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenylethyl)acetamide **57** (76.8 mg, 0.202 mmol) in $C_2H_4Cl_2$ (2.2 mL) was added to the catalyst $Rh_2(cap)_4$(1.3 mg, 1.98×10^{-3} mmol). The mixture was stirred under reflux

for 7 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-γ-lactam[41] **99** (54.4 mg, 76 %) and *trans*-4-benzyl-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-β-lactam **100** (2.1 mg, 3 %) as a mixture.

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **99** (80%) (*cis/trans*: 0.09/1), **100** (3%) (*cis/trans*: 2.3/1), **101** (<2%).

5.5.3.5. Reaction of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4(SIPr)$



Scheme 194

A solution of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide **45** (93.3 mg, 0.325 mmol) in $C_2H_4Cl_2$ (9.4 mL) was added to the catalyst $Rh_2(OAc)_4(SIPr)$ (3.0 mg, 3.61×10^{-3} mmol). The mixture was stirred under reflux for 6 h. The solvent was removed under reduced pressure and a ^1H NMR spectra was taken. The residue was purified through silica preparative TLC (10 % AcOEt in toluene) providing *trans*-3-acetyl-1-(*tert*-butyl)-4-phenyl-γ-lactam[39] **47** (15.0 mg, 18 %) and *trans*-3-acetyl-4-benzyl-1-(*tert*-butyl)-β-lactam[39] **46** (11.8 mg, 14 %).

^1H NMR to the reactional mixture (300 MHz, $CDCl_3$): **47** (32%), **46** (39%), **103** (29%).

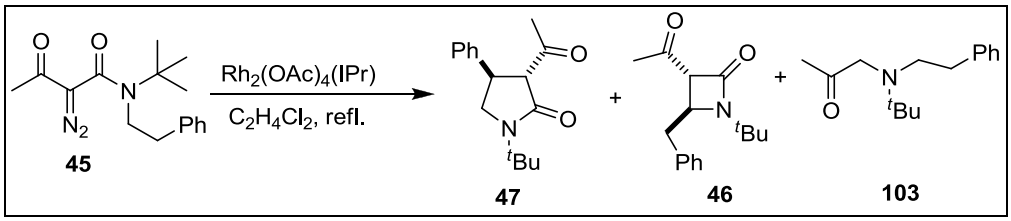
trans-3-acetyl-1-(*tert*-butyl)-4-phenyl-γ-lactam **47**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H, NC(CH_3)$_3$), 2.40 (s, 3H, CH_3CO), 3.41 (dd, J=6.3 Hz, J=9.3 Hz, 1H, CHPhC*H*HN), 3.70 (d, J=7.6 Hz, 1H, COC*H*), 3.84-3.98 (m, 2H, CHPhCH*H*N, PhC*H*), 7.15-7.32 (m, 5H, *Ph*).

trans-3-acetyl-4-benzyl-1-(*tert*-butyl)-β-lactam **46**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H, NC(CH_3)$_3$), 2.07 (s, 3H, CH_3CO), 2.67 (dd, J=10.4 Hz, J=14.0, Hz, 1H, , PhC*H*HC), 3.39 (dd, J=4.4 Hz, J=14.0 Hz, 1H, PhCH*H*C), 3.50 (d, J=2.0 Hz, 1H, CH_2C*H*CO), 4.30 (ddd, J=2.0 Hz, J=4.4 Hz, J=10.4 Hz, 1H, NC*H*CH_2), 7.15-7.29 (m, 5H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): 28.43 (s, 9H, NC(CH_3)$_3$); 29.95 (CH_3CO); 40.51; 52.59; 54.64 (N*C*(CH_3)$_3$); 66.14 (CO*C*HCO); 126.98, 128.52, 128.81, 136.56 (*Ph*); 162.14 (N*C*O); 200.28 (CH_3*C*O).

5.5.3.6. Reaction of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4$(IPr)



Scheme 195

A solution of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide **45** (87.2 mg, 0.304 mmol) in $C_2H_4Cl_2$ (9.4 mL) was added to the catalyst $Rh_2(OAc)_4$(IPr) (3.0 mg, 3.61×10^{-3} mmol). The mixture was stirred under reflux for 6 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was purified through silica preparative TLC (10 % AcOEt in toluene) providing *trans*-3-acetyl-1-(*tert*-butyl)-4-phenyl-γ-lactam[39] **47** (14.5 mg, 17 %), *trans*-3-acetyl-4-benzyl-1-(*tert*-butyl)-β-lactam[39] **46** (26.2 mg, 35 %) and N-(*tert*-butyl)-N-phenylethyl-(methyl-acetyl)-amine (5.7 mg, 7 %) **103**, being this last compound contaminated with **47**.

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **47** (18%), **46** (46%), **103** (36%).

In order to isolate N-(tert-butyl)-N-phenylethyl-(methyl-acetyl)-amine **103** the reaction mixture was purified by basic alumina preparative TLC:

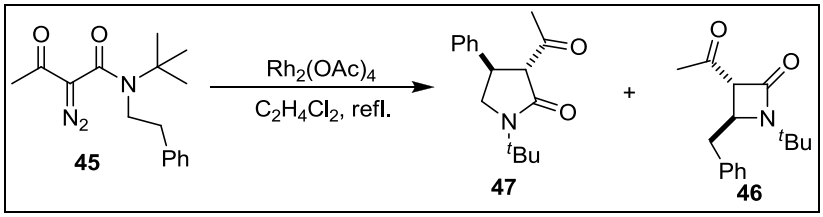
A solution of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide **45** (90.4 mg, 0.315 mmol) in $C_2H_4Cl_2$ (9.4 mL) was added to the catalyst $Rh_2(OAc)_4(IPr)$ (3.3 mg, 3.97×10^{-3} mmol). The mixture was stirred under reflux for 6 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was purified through basic alumina preparative TLC (9 % AcOEt in hexanes) providing N-(*tert*-butyl)-N-phenylethyl-(methyl-acetyl)-amine (12.2 mg, 17 %) **103** as a colorless liquid.

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **47** (23%), **46** (46%), **103** (31%).

N-(*tert*-butyl)-N-phenylethyl-(methyl-acetyl)-amine **103**:

Decomposes easily even under Ar in the freezer.
R_f = 0.81 (neutral alumina, 20 % AcOEt in hexanes).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 9H, $NC(CH_3)_3$), 2.24 (s, 3H, $COCH_3$), 2.70-2.80 (m, 4H, $PhCH_2CH_2N$), 3.30 (s, 2H, $COCH_2N$), 7.18-7.30 (m, 5H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 26.97 ($NC(CH_3)_3$), 27.11($COCH_3$), 37.25 ($PhCH_2CH_2N$), 53.71 ($PhCH_2CH_2N$), 55.35 ($NC(CH_3)_3$), 61.81 ($COCH_2N$), 126.04, 128.38, 128.71, 140.22 (*Ph*), 212.15 (CH_3COCH_2).
IR (neat, cm^{-1}): 2971 (C-H), 1709 (C=O), 1652, 1363, 1222

5.5.3.7. **Reaction of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4$**

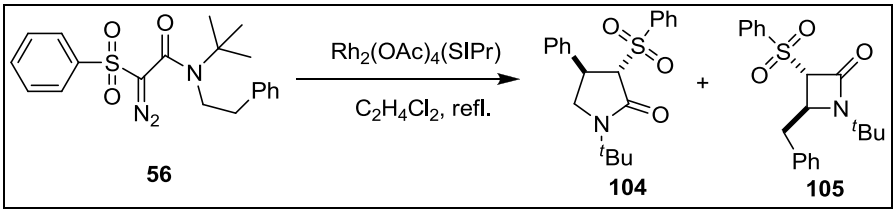


Scheme 196

A solution of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide **45** (86.6 mg, 0.302 mmol) in $C_2H_4Cl_2$ (9.4 mL) was added to the catalyst $Rh_2(OAc)_4$ (1.9 mg, 3.84×10^{-3} mmol). The mixture was stirred under reflux for 6 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was purified through silica preparative TLC (15 % AcOEt in hexanes) providing *trans*-3-acetyl-1-(*tert*-butyl)-4-phenyl-γ-lactam[39] **47** (36.8 mg, 47 %) and *trans*-3-acetyl-4-benzyl-1-(*tert*-butyl)-β-lactam[39] **46** (19.6 mg, 25 %).

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **47** (65%) and **46** (34%).

5.5.3.8. **Reaction of N-(tert-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4$(SIPr) in $C_2H_4Cl_2$.**



Scheme 197

A solution of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide **56** (120.6 mg, 0.313 mmol) in $C_2H_4Cl_2$ (3.5mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (6.5 mg, 7.81×10^{-3} mmol). The mixture was stirred under reflux for 4 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was purified through silica preparative TLC (1.5 : 4 : 4 AcOEt : Hexanes :

Toluene) providing *trans*-1-(*tert*-butyl)-4-phenyl-3-(phenylsulfonyl)-γ-lactam[42] **104** (60.3 mg, 54 %) and *trans*-4-benzyl-1-(*tert*-butyl)-3-(phenylsulfonyl)-β-lactam **105** (23.6 mg, 21 %) as a white solid.

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **104** (64%) and **105** (30%).

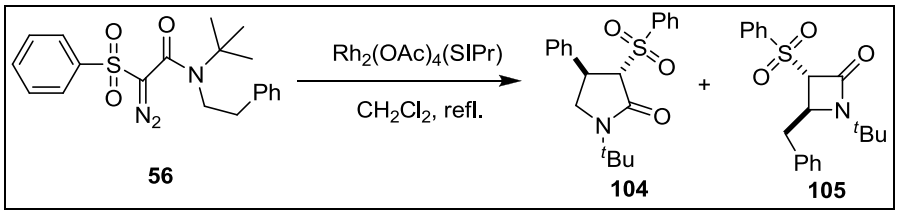
trans-1-(*tert*-butyl)-4-phenyl-3-(phenylsulfonyl)-γ-lactam[42] **104**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H, NC(C*H*$_3$)$_3$), 3.53 (dd, J=2.1 Hz, J=9.7 Hz, 1H, NCH*H*CHPh), 3.89 (d, J=3.0 Hz, 1H, SC*H*CO), 4.02-4.13 (m, 2H, overlapped signals, NC*H*HCHPh, ArC*H*CH$_2$) 7.19-7.36 (m, 5H, *Ph*), 7.53-7.57 (m, 2H, *Ph*), 7.64-7.68 (m, 1H, *Ph*), 7.91-7.93 (m, 2H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 27.31 (NC(*C*H$_3$)$_3$), 37.02 (*C*HArCH$_2$N), 51.82 (CHPh*C*H$_2$N), 55.24 (N*C*(CH$_3$)$_3$), 74.94 (S*C*CO), 126.39, 127.74, 128.93, 129.32, 134.14, 137.81, 142.36 (*Ph*), 164.88 (*C*=O).

trans-4-benzyl-1-(*tert*-butyl)-3-(phenylsulfonyl)-β-lactam **105**:

m. p.= 132-135 ºC.
R$_f$ = 0.12 (silica, 20 % AcOEt in hexanes).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H, NC(C*H*$_3$)$_3$), 2.80 (dd, J= 8.6 Hz, J=14.0 Hz, 1H, PhC*H*HC), 3.30 (dd, J=4.2 Hz, J=14.0 Hz, 1H, PhCH*H*C), 4.09 (d, J=2.0 Hz, 1H, SC*H*CO), 4.26 (ddd, J=2.0 Hz, J=4.2 Hz, J=8.6 Hz, 1H, NC*H*CH$_2$S), 7.11-7.14 (m, 2H, *Ph*), 7.22-7.30 (m, 3H, *Ph*), 7.46-7.50 (m, 2H, *Ph*), 7.59-7.63 (m, 1H, *Ph*), 7.81-7.84 (m, 2H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 28.19 (NC(*C*H$_3$)$_3$), 40.22 (Ph*C*H$_2$CH), 53.87 (PhCH$_2$*C*HN), 55.40 (N*C*(CH$_3$)$_3$), 72.45 (S*C*HCO), 127.41, 128.84, 128.90, 129.04, 129.11, 134.16, 135.08, 137.73 (*Ph*), 157.66 (*C*O).
IR (neat, cm^{-1}): 2974 (C-H), 1754 (C=O), 1151 (S=O), 1084.
MS (FAB$^+$) *m/z*: 358, 259, 207, 154.
HMRS (FAB$^+$): *m/z* calcd. [M+H]$^+$= 358.147691, found [M+H]$^+$: 358.147979.

5.5.3.9. Reaction of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4$(SIPr) in CH_2Cl_2.

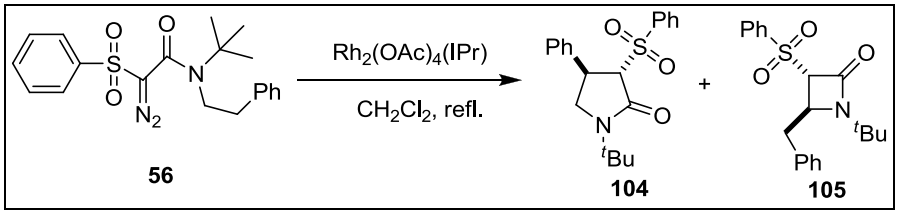


Scheme 198

A solution of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide **56** (121.0 mg, 0.315 mmol) in CH_2Cl_2 (3.5mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (6.4 mg, 7.69×10^{-3} mmol). The mixture was stirred under reflux for 53 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was purified through silica preparative TLC (1.5 : 4 : 4 AcOEt : Hexanes : Toluene) providing *trans*-1-(*tert*-butyl)-4-phenyl-3-(phenylsulfonyl)-γ-lactam[42] **104** (43.2 mg, 67 %) and *trans*-4-benzyl-1-(*tert*-butyl)-3-(phenylsulfonyl)-β-lactam **105** (5.4 mg, 5 %).

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **104** (89%) and **105** (8%).

5.5.3.10. Reaction of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4$(IPr) in CH_2Cl_2.

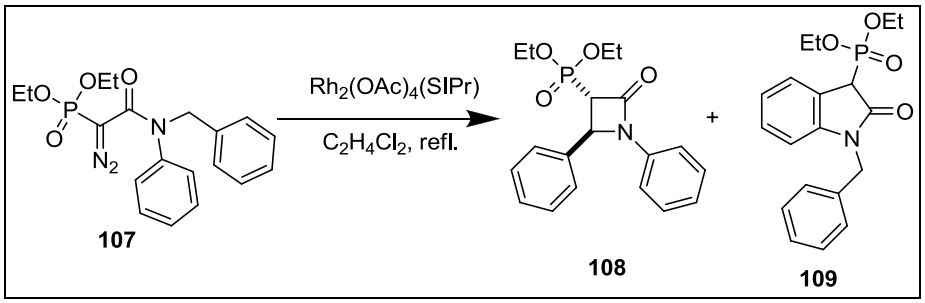


Scheme 199

A solution of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(phenylethyl)acetamide **56** (118.1 mg, 0.307 mmol) in CH_2Cl_2 (3.5mL) was added to the catalyst $Rh_2(OAc)_4$(IPr) (6.2 mg, 7.45×10^{-3} mmol). The mixture was stirred under reflux for 53 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken.

The residue was purified through silica preparative TLC (1.5 : 4 : 4 AcOEt : Hexanes : Toluene) providing *trans*-1-(*tert*-butyl)-4-phenyl-3-(phenylsulfonyl)-γ-lactam[42] **104** (77.1 mg, 70 %) and *trans*-4-benzyl-1-(*tert*-butyl)-3-(phenylsulfonyl)-β-lactam **105** (12.9 mg, 12 %).

5.5.3.11. **Reaction of N-(benzyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenyl)acetamide with $Rh_2(OAc)_4(SIPr)$**

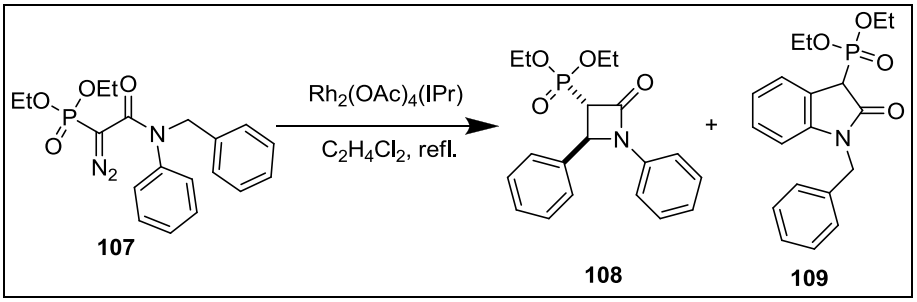


Scheme 200

A solution of N-(benzyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenyl)acetamide[41] **107** (49.3 mg, 0.127 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4(SIPr)$ (1.2 mg, 1.44×10^{-3} mmol). The mixture was stirred under reflux for 53 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through a celite pad (50 % AcOEt in hexanes) providing 1-benzyl-3-(diethoxyphosphoryl)indolin-2-one[41] **109** (34.8 mg, 76 %), *trans*-1,4-diphenyl-3-(diethoxyphosphoryl)-β-lactam[41] **108** (5.5 mg, 12 %) as a mixture.

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **109** (85%), **108** (12%, 100 % *trans*).

5.5.3.12. **Reaction of N-(benzyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenyl)acetamide with $Rh_2(OAc)_4$(IPr)**

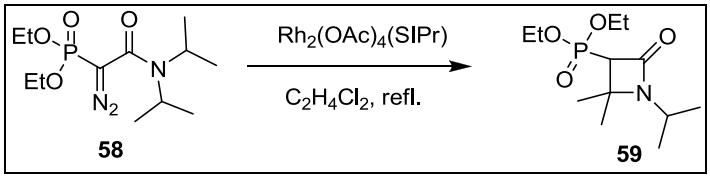


Scheme 201

A solution of N-(benzyl)-2-diazo-2-(diethoxyphosphoryl)-N-(phenyl)acetamide[41] **107** (45.2 mg, 0.117 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4$(IPr) (1.3 mg, 1.56×10^{-3} mmol). The mixture was stirred under reflux for 53 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through a celite pad (50 % AcOEt in hexanes) providing 1-benzyl-3-(diethoxyphosphoryl)indolin-2-one[41] **109** (32.6 mg, 80 %), *trans*-1,4-diphenyl-3-(diethoxyphosphoryl)-β-lactam[41] **108** (3.2 mg, 6 %) as a mixture.

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **109** (90%), **108** (7%) (100 % *trans*).

5.5.3.13. **Reaction of 2-diazo-2-(diethoxyphosphoryl)-N-(diisopropyl)acetamide with $Rh_2(OAc)_4$(SIPr)**



Scheme 202

A solution of 2-diazo-2-(diethoxyphosphoryl)-N-(diisopropyl)acetamide[41] **58** (38.4 mg, 0.126 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (1.0 mg, 1.20×10^{-3} mmol). The mixture was stirred under reflux for 21 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was

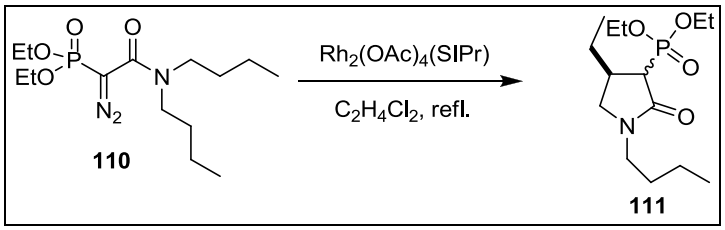
purified through a basic alumina flash chromatography (50 % AcOEt in hexanes) providing 1-isopropyl-3-(diethoxyphosphoryl)-4,4-dimethyl-β-lactam[41] **59** (28.0 mg, 80 %).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **59** (88%)

1-isopropyl-3-(diethoxyphosphoryl)-4,4-dimethyl-β-lactam **59**:

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29-1.31 (m, 12H, overlapped signals, OCH_2CH_3 and $NCH(CH_3)_2$), 1.44 (s, 3H, $CHC(CH_3)_2N$), 1.59 (s, 3H, $CHC(CH_3)_2N$), 3.22 (d, $J_{H\text{-}P}$=17.4 Hz, 1H, POCHCO), 3.46-3.55 (m, 1H, $NCH(CH_3)_2$), 4.08-4.26 (m, 4H, OCH_2CH_3).
^{31}P NMR (120 MHz, $CDCl_3$): 18.80.

5.5.3.14. Reaction of 2-diazo-1,1-dibutyl-2-(diethoxyphosphoryl)-N-acetamide with $Rh_2(OAc)_4$(SIPr)

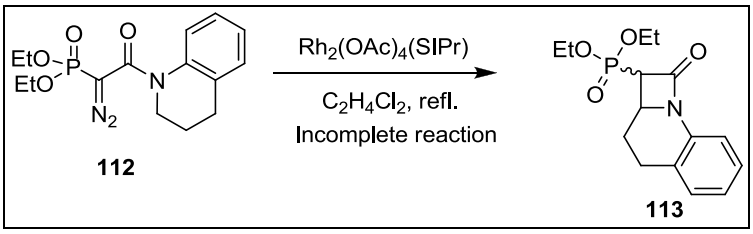


Scheme 203

A solution of 2-diazo-1,1-dibutyl-2-(diethoxyphosphoryl)-N-acetamide [41] **110** (43.0 mg, 0.132 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (1.3 mg, 1.56×10^{-3} mmol). The mixture was stirred under reflux for 16 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through a basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-butyl-4-ethyl-3-(diethoxyphosphoryl)-β-lactam[41] **111** (35.7 mg, 89 %).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **111** (93 %, *cis*/*trans*: 0.07/1).

5.5.3.15. **Reaction of 2-diazo-2-(diethoxyphosphoryl)-N-(tetrahydroquinoline)acetamide with $Rh_2(OAc)_4$(SIPr)**

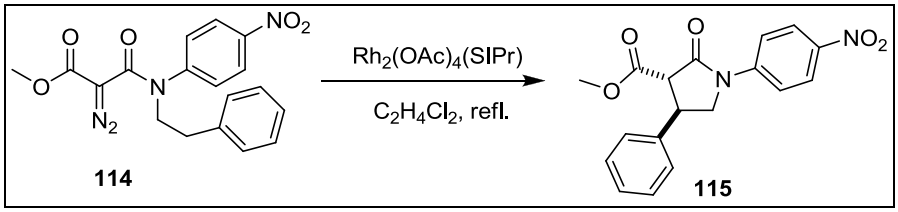


Scheme 204

A solution of 2-diazo-2-(diethoxyphosphoryl)-N-(tetrahydroquinoline)acetamide[41] **112** (38.3 mg, 0.114 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (1.1 mg, 1.32×10^{-3} mmol). The mixture was stirred under reflux for 70 h being the reaction still incomplete (TLC). The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through a basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-β-lactam[41] **113** (9.6 mg, 41 %) and reagent 2-diazo-2-(diethoxyphosphoryl)-N-(tetrahydroquinoline)acetamide **112** (10.5 mg, 41) as a mixture.

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **112** (48 %), **113** (47 %).

5.5.3.16. **Reaction of 2-(carbomethoxy)-2-diazo-N-(*p*-nitrophenyl)acetamide with $Rh_2(OAc)_4$(SIPr)**



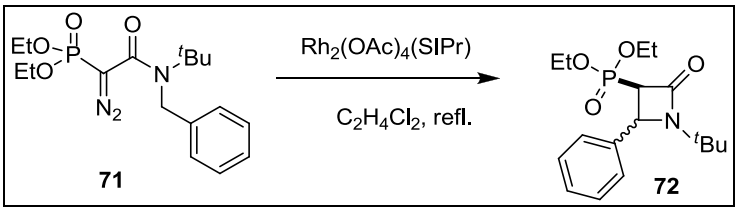
Scheme 205

A solution of 2-(carbomethoxy)-2-diazo-N-(*p*-nitrophenyl)acetamide[134] **114** (47.2 mg, 0.128 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (1.2 mg, 1.44×10^{-3} mmol). The mixture was stirred under reflux for 24 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was

purified through silica preparative TLC (20 % AcOEt in toluene) providing *trans*-3-carbomethoxy-4-phenyl-N-(*p*-nitrophenyl)-γ-lactam[134] **115** (43.0 mg, 98 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.90-4.02 (m, 2H, overlapped signals, NC*H*HCH, CH_2CHPh), 4.11-4.20 (m, 1H, COC*H*CO), 4.32 (t, J= 8.4 Hz, 1H, NCH*H*CH), 7.30-7.48 (m, 5H, *Ph*), 7.85 (d, J=9.3 Hz, 2H, $C(CH)_4CNO_2$), 8.25 (d, J= 9.3 Hz, 2H, $C(CH)_4CNO_2$).

5.5.3.17. **Reaction of N-benzyl-N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)acetamide with $Rh_2(OAc)_4$(SIPr)**

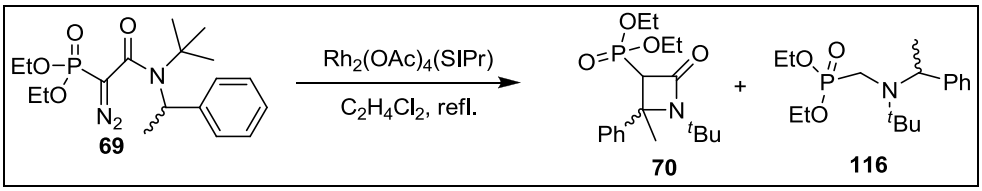


Scheme 206

A solution of N-benzyl-N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)acetamide **71** (47.7 mg, 0.130 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) (1.0 mg, 1.20×10^{-3} mmol). The mixture was stirred under reflux for 47 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-β-lactam **72** (37.1 mg, 84 %).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **72** (87 %) (*cis/trans*: 1/0.22).

5.5.3.18. **Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4(SIPr)$**



Scheme 207

A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (54.0 mg, 0.142 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4(SIPr)$ (1.1 mg, 1.32×10^{-3} mmol). The mixture was stirred under reflux for 25 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-β-lactam **70** (8.4 mg, 17 %) and N-(*tert*-butyl)-N-(2-phenylethyl)-(methyl-diethoxyphosphoryl)-amine **116** (20.4 mg, 44%).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **70** (23%) (*cis/trans*: 0.63/1), **116** (51%).

trans-4-phenyl-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-β-lactam **70**:

^1H NMR (300 MHz, $CDCl_3$): δ 1.30-1.37 (m, overlapped signals, 15H, OCH_2CH_3 and $NC(CH_3)_3$), 2.21 (s, 3H, $C(CH_3)Ph$), 3.43 (d, J_{P-H}= 17.4 Hz, 1H, POCHCO), 4.10-4.30 (m, 4H, OCH_2CH_3), 7.27-7.82 (m, 5H, $C(CH_3)Ph$).
^{31}P NMR (120 MHz, $CDCl_3$): δ 17.48.

N-(*tert*-butyl)-N-(2-phenylethyl)-(methyl-diethoxyphosphoryl)-amine **116**:

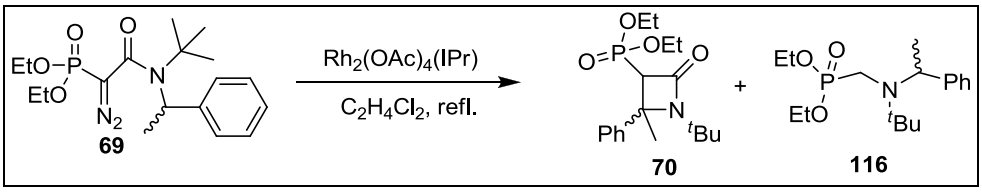
R_f = 0.76 (neutral alumina, 30 % AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (s, 9H, NC(CH_3)$_3$), 1.24, 1.26 (t, J= 7.0 Hz, 6H, OCH$_2$*CH$_3$*), 1.51 (d, J= 7.2 Hz, 3H, NC*H$_3$*CHPh), 3.04-3.18 (m, 2H, PC*H$_2$*N), 3.93-4.07 (m, 4H, OC*H$_2$*CH$_3$), 4.40 (q, J=7.2 Hz, 1H, NCH$_3$C*H*Ph), 7.16-7.51 (m, 5H, *Ph*).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.38, 16.43 (OCH$_2$*C*H$_3$), 18.64 (N*C*H$_3$CHPh), 28.87 (NC(*C*H$_3$)$_3$), 42.26 (d, J_{P-C}=171.7 Hz, P*C*H$_2$N), 56.01 (NCH$_3$*C*HPh), 56.73 (N*C*(CH$_3$)$_3$), 61.40, 61.59 (O*C*H$_2$CH$_3$), 126.04, 127.73, 127.80, 146.37 (*Ph*).

^{31}P-NMR (160 MHz, $CDCl_3$): δ 27.89.

5.5.3.19. Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4(IPr)$

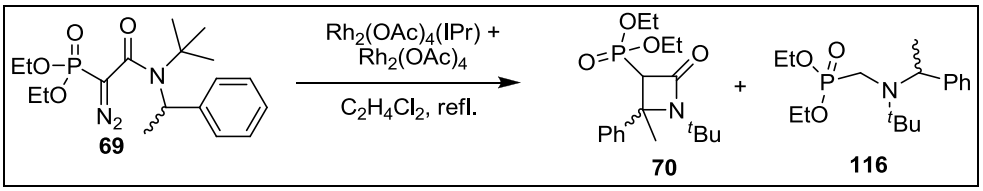


Scheme 208

A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (53.2 mg, 0.140 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4(IPr)$ (1.1 mg, 1.32×10^{-3} mmol). The mixture was stirred under reflux for 25 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-β-lactam **70** (6.2 mg, 15 %) and N-(*tert*-butyl)-N-(2-phenylethyl)-(methyl-diethoxyphosphoryl)-amine **116** (21.5 mg, 47%).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **70** (19%) (*cis/trans*: 0.44/1), **116** (57%).

5.5.3.20. **Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4(IPr)$ and $Rh_2(OAc)_4$**

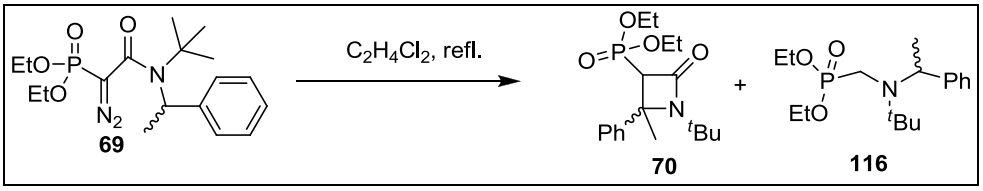


Scheme 209

A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (19.8 mg, 0.0520 mmol) in $C_2H_4Cl_2$ (0.6 mL) was added to catalysts $Rh_2(OAc)_4(IPr)$ (0.8 mg, 0.96×10^{-3} mmol) and $Rh_2(OAc)_4$ (0.4 mg, 0.91×10^{-3} mmol). The mixture was stirred under reflux for 3 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-β-lactam **70** (10.2 mg, 56 %) and N-(*tert*-butyl)-N-(2-phenylethyl)-(methyl-diethoxyphosphoryl)-amine **116** (2.2 mg, 13%).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **70** (19%) (*cis/trans*: 0.44/1), **116** (57%).

5.5.3.21. **Thermal decomposition of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide**



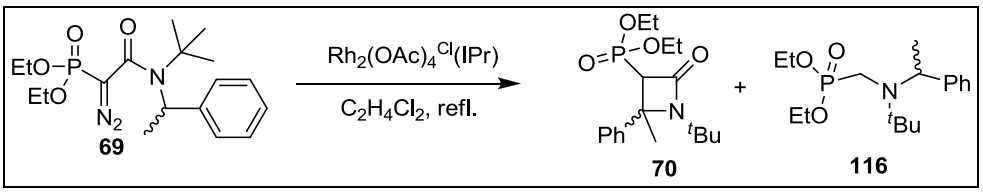
Scheme 210

A solution of N-(tert-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (42.6 mg, 0.109 mmol) in $C_2H_4Cl_2$ (1.4 mL) was stirred under reflux for 25 h. The solvent was removed under reduced pressure and a ^{13}P NMR

spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **70** (33%) (*cis/trans*: 0.31/1), **116** (17%).

5.5.3.22. Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4^{Cl}$(IPr)

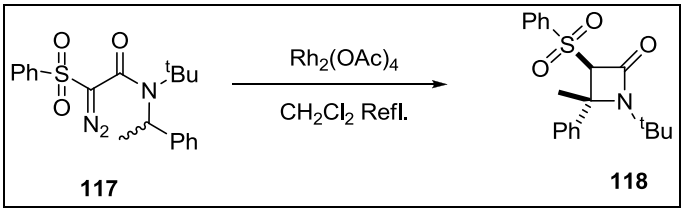


Scheme 211

A solution of N-(tert-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (46.2 mg, 0.121 mmol) in $C_2H_4Cl_2$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4^{Cl}$(IPr) (1.1 mg, 1.22×10^{-3} mmol). The mixture was stirred under reflux for 20 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina flash chromatography (50 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-β-lactam **70** (4.7 mg, 11 %) and N-(*tert*-butyl)-N-(2-phenylethyl)-(methyl-diethoxyphosphoryl)-amine **116** (15.9 mg, 40%).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **70** (19%) (*cis/trans*: 0.44/1), **116** (57%).

5.5.3.23. Reaction of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4$



117 118

Scheme 212

A solution of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide **117** (49.2 mg, 0.127 mmol) in CH_2Cl_2 (1.4 mL) was added to the catalyst $Rh_2(OAc)_4$ (1.6 mg, 3.62×10^{-3} mmol). The mixture was stirred under reflux for 2.5 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was purified through silica preparative TLC (30 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(phenylsulfonyl)-4-phenyl-β-lactam **118** (15.0 mg, 33 %) as a white solid.

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **118** (39%).

trans-1-(*tert*-butyl)-3-(phenylsulfonyl)-4-phenyl-β-lactam **118**:

R_f = 0.18 (neutral alumina, 20 % AcOEt in hexanes).

m. p.= 134-138 ºC

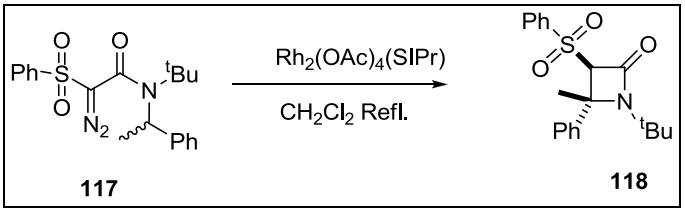
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H, NC(CH_3)$_3$), 2.52 (s, 3H, CH_3C(Ph)N), 4.24 (s, 1H, SO_2CHCO), 7.34-7.47 (m, 3H, *Ph*), 7.49-7.51 (m, 2H, *Ph*), 7.55-7.59 (m, 2H, *Ph*), 7.64-7.71 (m, 1H, *Ph*), 8.04-8.07(m, 2H, *Ph*).

^{13}C NMR (100MHz, $CDCl_3$): 20.12 (CH_3C(Ph)N), 28.41 (NC(CH_3)$_3$), 56.76 (NC(CH_3)$_3$), 65.24 (CH_3C(Ph)N), 79.60 (SO_2CHCO), 125.35, 128.28, 128.90, 129.00, 129.08, 134.19, 139.88, 142.92 (*Ph*), 159.39 (CO)

IR (neat, cm^{-1}): 2980, 1751, 1319, 1150, 1084.

X-ray diffraction: An ORTEP diagram from single crystal can be found on Scheme 58, its coordinates attached

5.5.3.24. Reaction of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4(SIPr)$



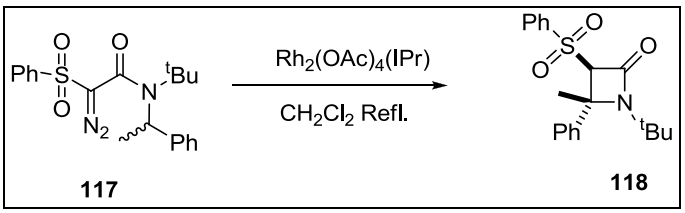
117 118

Scheme 213

A solution of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide **117** (49.2 mg, 0.127 mmol) in CH_2Cl_2 (1.5 mL) was added to the catalyst $Rh_2(OAc)_4(SIPr)$ (2.6 mg, 3.11×10^{-3} mmol). The mixture was stirred under reflux for 120 h. The solvent was removed under reduced pressure and a ^1H NMR spectra was taken. The residue was purified through silica preparative TLC (20 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(phenylsulfonyl)-4-phenyl-β-lactam **118** (23.6 mg, 52 %).

^1H NMR to the reactional mixture (300 MHz, $CDCl_3$): **118** (60%).

5.5.3.25. Reaction of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4(IPr)$



117 118

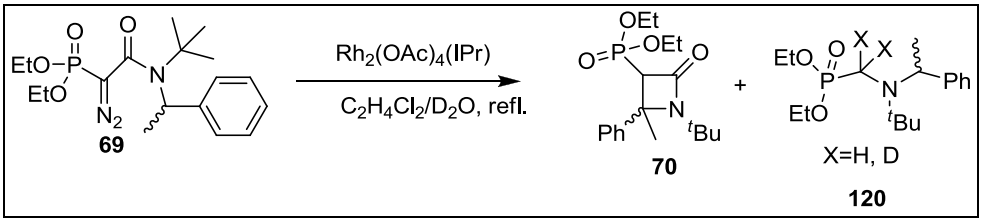
Scheme 214

A solution of N-(*tert*-butyl)-2-diazo-2-(phenylsulfonyl)-N-(2-phenylethyl)acetamide **117** (49.2 mg, 0.127 mmol) in CH_2Cl_2 (1.5 mL) was added to the catalyst $Rh_2(OAc)_4(SIPr)$ (2.7 mg, 3.24×10^{-3} mmol). The mixture was stirred under reflux for 120 h. The solvent was removed under reduced pressure and a ^1H NMR spectra was taken. The residue was purified through silica preparative TLC (20 % AcOEt in

hexanes) providing *trans*-1-(*tert*-butyl)-3-(phenylsulfonyl)-4-phenyl-β-lactam **118** (23.1 mg, 51 %).

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **118** (60%).

5.5.3.26. Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4(IPr)$ in $C_2H_4Cl_2$ saturated with D_2O



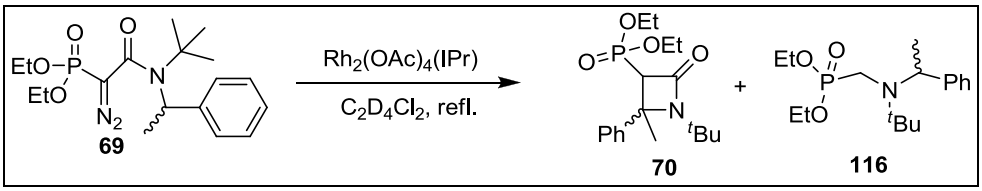
Scheme 215

1,2-dicloroethane (3 mL) and D_2O (300 μL) were equilibrated during 11 days. Then 1.4 mL of the organic phase were used for this reaction. A solution of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (44.5 mg, 0.117 mmol) in $C_2H_4Cl_2/D_2O$ (1.4 mL) was added to the catalyst $Rh_2(OAc)_4(IPr)$ (1.4 mg, 1.17×10^{-3} mmol). The mixture was stirred under reflux for 24 h. The solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina preparative TLC (40 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-β-lactam **70** (6.2 mg, 15 %) and N-(*tert*-butyl)-N-(2-phenylethyl)-(methyl-diethoxyphosphoryl)-amine **120** (19.1 mg, 50 %).

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **70** (16%), **120** (59%).

Mono- and di-deuterated **120**: The ^{31}P NMR (160 MHz) revealed peaks at 28.05 (di-deuterated), 27.98 (mono-deuterated), besides the regular 27.09. The ^{1}H NMR integration also displayed 1.3 H instead of 2 H for the α-phosphoryl protons.

5.5.3.27. **Reaction of N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide with $Rh_2(OAc)_4$(IPr) in $C_2D_4Cl_2$**

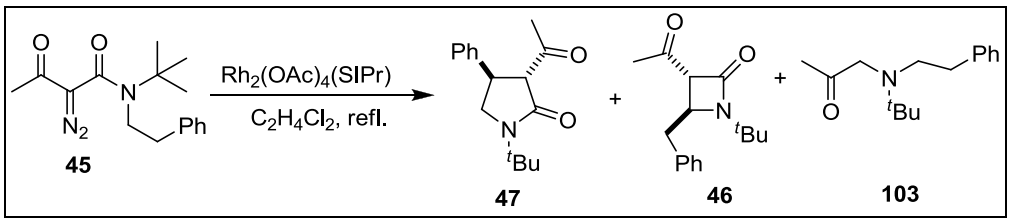


Scheme 216

A sealed glass ampoule containing N-(*tert*-butyl)-2-diazo-2-(diethoxyphosphoryl)-N-(2-phenylethyl)acetamide **69** (54.4 mg, 0.143 mmol), $C_2D_4Cl_2$ (265 mg) and the catalyst $Rh_2(OAc)_4$(IPr) (1.3 mg, 1.56×10^{-3} mmol) under Argon, was introduced into a glass reactor containing 1,2-dichloroethane. The mixture was refluxed for 24 h. Then the ampoule was opened, the solvent was removed under reduced pressure and a ^{13}P NMR spectra was taken. The residue was purified through basic alumina preparative TLC (40 % AcOEt in hexanes) providing *trans*-1-(*tert*-butyl)-3-(diethoxyphosphoryl)-4-phenyl-β-lactam **70** (2.5 mg, 5 %) and N-(*tert*-butyl)-N-(2-phenylethyl)-(methyl-diethoxyphosphoryl)-amine **116** (13.1mg, 28%). The ^1H and ^{13}P NMR were similar to the already obtained non deuterated product **116**.

^{31}P NMR to the reactional mixture (120 MHz, $CDCl_3$): **70** (27%), **116** (60%).

5.5.3.28. **Reaction of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide with $Rh_2(OAc)_4$(SIPr) for catalyst recovery**



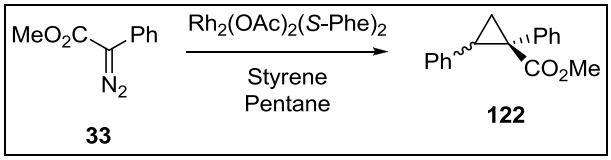
Scheme 217

A solution of N-(*tert*-butyl)-2-diazo-2-(acetyl)-N-(phenylethyl)acetamide **45** (94.3 mg, 0.329 mmol) in $C_2H_4Cl_2$ (9.4 mL) was added to the catalyst $Rh_2(OAc)_4$(SIPr) **89**

(10.2 mg, 12.2 × 10^{-3} mmol). The mixture was stirred under reflux for 4.5 h. The solvent was removed under reduced pressure and a ^{1}H NMR spectra was taken. The residue was purified through silica preparative TLC (20 % AcOEt in toluene) where the catalyst $Rh_2(OAc)_4$(SIPr) **89** (5.7 mg, 56 %) was recovered with the same spectral data.

^{1}H NMR to the reactional mixture (300 MHz, $CDCl_3$): **47** (27%), **46** (41%), **103** (32%).

5.5.3.29. Styrene cyclopropanation of methyl phenyldiazoacetate with $Rh_2(OAc)_2$(*S*-Phe)$_2$



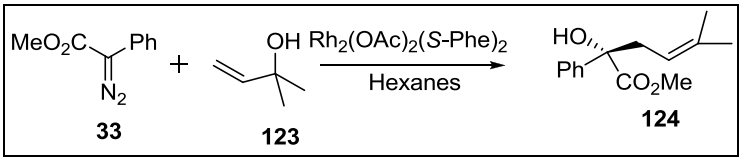
33 **122**

Scheme 218

Methyl phenyldiazoacetate **33** (57.6 mg, 0.325 mmol) dissolved in pentane (1.5 mL) was added during 1.5 h with a syringe pump to $Rh_2(OAc)_2$(*S*-Phe)$_2$ **96** (4.2 mg, 6.4 × 10^{-3} mmol), styrene (110.3 mg, 1.06 mmol) and activated powder molecular sieves 4Å (262 mg) in pentane (1.5 mL). After 20 h the solvent was evaporated and the reaction mixture was purified through silica preparative TLC (10 % AcOEt in hexanes) providing the racemic methyl 1,2-diphenylcyclopropanecarboxylate **112**[58] (52.9 mg, 65 %). The *ee* was determined by chiral HPLC with a Phenomenex Lux column, 1.5 % *iso*propanol in hexanes, 0.7 ml/min, λ=254 nm, R_t= 11.00 min. and R_t= 11.68 min- *ee*= 0%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94 (dd, J = 4.8 Hz, J= 7.5 Hz, 1H), 2.20 (dd, J = 4.8 Hz, J= 9.3 Hz, 1H), 3.19 (dd, J = 7.2 Hz, J= 9.3 Hz, 1H), 3.71 (s, 3H, COOC*H*$_3$), 6.81-6.85 (m, 2H, *Ph*); 7.08-7.18 (m, 8H, *Ph*).

5.5.3.30. $Rh_2(OAc)_2$(*S*-Phe)$_2$ catalyzed reaction of methyl phenyldiazoacetate with OH insertion/[2,3] sigmatropic rearrangement

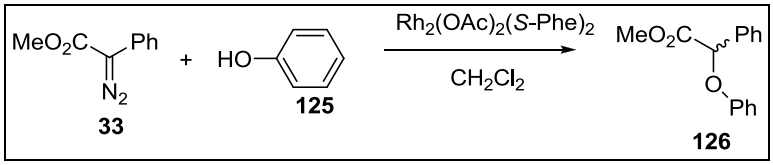


Scheme 219

Methyl phenyldiazoacetate **33** (104.2 mg, 0.592 mmol) dissolved in pentane (5 mL) was added during 1 h with a syringe pump to $Rh_2(OAc)_2$(*S*-Phe)$_2$ (3.8 mg, 5.8×10^{-3} mmol), 2-methyl-3-buten-2-ol **123** (0.23 mL, 2.2 mmol) in refluxing hexanes (1mL). After refluxing 22 h, the solvent was removed under reduced pressure and purified through silica preperative TLC (10 % AcOEt in hexanes) providing (*S*)-methyl 2-hydroxy-5-methyl-2-phenylhex-4-enoate **124**[59] (30.7 mg, 22 %). The *ee* was determined by chiral HPLC with a Chiralpack OD column, 0.5 % *iso*propanol in hexanes, 0.7 mL/min, λ=230 nm, R_t= 17.2 min. (minor) and R_t= 18.4 min. (major) - *ee*= 23% *S*-enantiomer[59].

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 3H), 1.72 (s, 3H), 2.69 (dd, J = 14.7 Hz, J= 6.9 Hz, 1H,); 2.98 (dd, J= 7.5 Hz, J= 14.4 Hz, 1H); 3.70 (s, 1H); 3.77 (s, 3H); 5.15-5.19 (m, 1H); 7.28-7.71 (m, 5H).

5.5.3.31. $Rh_2(OAc)_2$(*S*-Phe)$_2$ catalyzed reaction of methyl phenyldiazoacetate with OH insertion



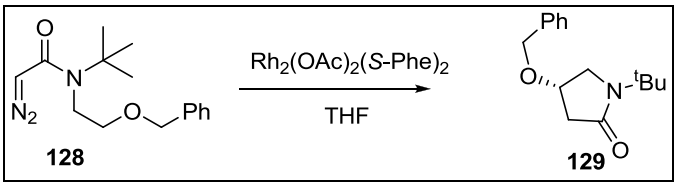
Scheme 220

Methyl phenyldiazoacetate **33** (56.9 mg, 0.324 mmol) dissolved in CH_2Cl_2 (1.5 mL) was added during 10 min with a syringe pump to $Rh_2(OAc)_2$(*S*-Phe)$_2$ (1.6 mg, $2.5 \times 10^{-}$

^{3} mmol), phenol **125** (41.4 mL, 2.2 mmol) in CH_2Cl_2 (2 mL). After 1 h, the solvent was removed under reduced pressure and purified through silica preperative TLC (10 % AcOEt in hexanes) providing methyl 2-phenoxy-2-phenylacetate **126**[60] (53.9 mg, 65 %). The *ee* was determined by chiral HPLC with a Chiralpack OD column, 10 % *iso*propanol in hexanes, 1 mL/min, λ=230 nm, R_t= 6.7min. and R_t= 7.6 min., *ee*= 0%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H, COOC*H*$_3$); 5.65 (s, 1H, OC*H*); 7.28-7.43 (m, 10H, *2Ph*).

5.5.3.32. Intramolecular C-H insertion catalyzed by $Rh_2(OAc)_2$(*S*-Phe)$_2$



Scheme 221

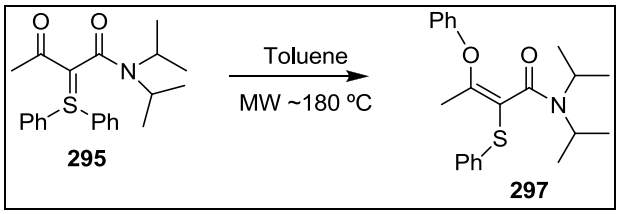
A solution of N-(2-Benzyloxyethyl)-N-*tert*-butyl-2-diazocetamide **128** (51.0 mg, 0.185 mmol) in THF (1mL) was added to the catalyst $Rh_2(OAc)_2$(*S*-Phe)$_2$ (1.4 mg, 2.2 × 10^{-3} mmol) in THF (1mL) during 10 min at RT. The mixture was stirred for 2h and the solvent was removed under reduced pressure. The residue was purified through silica preperative TLC (40% AcOEt in hexanes) providing 4-benzyloxy-1-*tert*-butylpyrrolidine-2-one[61] **129** (35 mg, 76%). The *ee* was determined by chiral HPLC with a Chiralpack AD column, 3 % *iso*propanol in hexanes, 1 mL/min, λ=254 nm, R_t= 15.6 min. and R_t= 16.8 min., *ee*= 0%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H); 2.46-2.66 (m, 2H); 3.48 (dd, J = 3.0 Hz, J= 9.6 Hz, 1H); 3.67 (dd, J = 6.3 Hz, J= 10.8 Hz, 1H); 4.0-4.15 (m, 1H); 4.51 (dd, J = 11.7 Hz, J= 29.1 Hz, 2H); 7.28-7.39 (m, 5H).

5.6. Diazo-Free C-H Insertion with C-C Bond Formation

5.6.1. Metal Carbenoid Formation Without Diazo Compounds

5.6.1.1. Thermal rearrangement of 2-(acetyl)-2-(diphenylsulfonium)-N-(di*iso*propyl)acetamide



Scheme 222

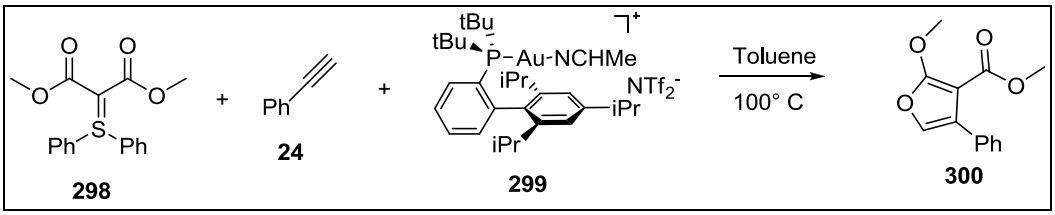
Following a general procedure[92].

2-(acetyl)-2-(diphenylsulfonium)-N-(di*iso*propyl)acetamide **295** (9.4 mg, 0.0254 mmol) in toluene 0.25 mL were heated in a closed MW tube for 3h under MW at ca. 180 ºC radiation. The solvent was evaporated and pure product **297** (8.6 mg, 92 %) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (bs, 12H, N(CH(CH_3)$_2$)$_2$); 2.00 (s, 3H, CH_3COPh), 3.27 (sp, J= 6.8 Hz, 1H, NC*H*); 4.30 (sp, J= 6.8 Hz, 1H, NC*H*); 6.99-7.00 (m, 2H, *Ph*); 7.07-7.14 (m, 1H, *Ph*); 7.20-7.36 (m, 5H, *Ph*); 7.55-7.57 (m, 2H, *Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.06 (CH_3COPh), 17.06 (bs, N(CH(CH_3)$_2$)$_2$), 45.68 (NCH), 51.01 (NCH), 117.40, 117.62, 122.97, 127.41, 128.55, 129.66, 132.43, 132.56, 149.47, 155.25 (Ph, *C*=*C*), 164.97 (NCO).

5.6.1.2. **Synthesis of methyl 2-methoxy-4-phenylfuran-3-carboxylate**



Scheme 223

A dry schlenk tube was charged with sulfonium ylide dimethyl-α-(diphenyltiomethylene)-malonate **298** (63.2 mg, 0.2 mmol), phenylacetylene **24** (110 μL, 1.0 mmol) and (acetonitrile)((2',4',6'-tri*iso*propyl-2-biphenyl)di-*tert*-butylphosphine)gold(I) bis(trifluoromethanesulfonyl)imide (9.0 mg, 0.01 mmol). The tube was evacuated and back filled with argon, and this procedure was repeated three times. The mixture was dissolved by dry toluene (1 mL), then stirred at 100 ºC for 4h. The mixture was cooled to room temperature, and another portion of (acetonitrile) ((2',4',6'-tri*iso*propyl-2-biphenyl)di-*tert*-butylphosphine)gold (I) bis(trifluoromethanesulfonyl)imide (9.0 mg, 0.01 mmol) was added to this mixture, and then the mixture was stirred at 100 ºC again for further 4h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified through silica flash chromatography (10 % AcOEt in pentane) where methyl 2-methoxy-4-phenylfuran-3-carboxylate **300** (31.4 mg, 68 %) was obtained as a pale yellow oil.

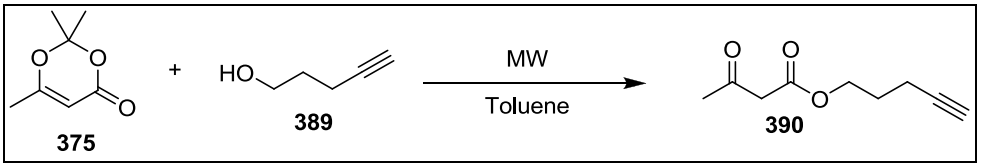
Spectra data identical to those reported[135].

R_f = 0.42 (silica, 20% AcOEt in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (s, 3H); 4.06 (s, 3H); 6.82 (s, 1H); 7.33-7.18 (m, 5H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 51.0, 57.8, 90.6, 127.5, 127.8, 128.2, 129.0, 129.6, 131.7, 163.1.

5.6.1.3. Synthesis of 2-acetyl-4-(pentylaceto)acetate

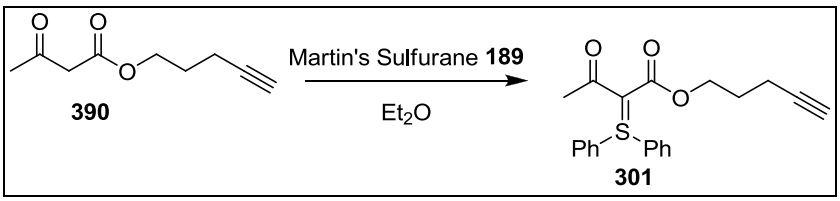


Scheme 224

4-Pentyn-1-ol **389** (130 μL, 1.41 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (186 μL, 1.41 mmol) were mixed in toluene (3 mL) and heated under MW at 160 ºC for 0.5 h. The solvent was removed under vacuum. The residue was purified through silica gel chromatography (20 % AcOEt in pentane) providing 2-acetyl-4-(pentylaceto)acetate **390** (170 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (p, J= 6.5 Hz, 2H, OCH_2CH_2); 1.96 (t, J= 2.5 Hz, 1H, $CHCCH_2$); 2.25 (s, 3H, CH_3CO); 2.28 (dt, J= 2.5 Hz, J= 7.0 Hz, 2H, $CHCCH_2CH_2$); 3.45 (s, 2H, $COCH_2CO$); 4.24 (t, J= 6.0 Hz, 2H, OCH_2).
^{13}C NMR (125 MHz, $CDCl_3$): δ 15.08 ($CHCCH_2$), 27.30 (OCH_2CH_2), 30.17 (CH_3CO), 50.00 ($COCH_2CO$), 63.82 (OCH_2), 69.19 ($CHCCH_2$), 82.76 ($CHCCH_2$), 167.04 (OCO), 200.48 (CH_3CO)

5.6.1.4. Synthesis of 2-acetyl-2-(diphenyltiomethylene)-4-(pentylaceto)acetate



Scheme 225

2-Acetyl-4-(pentylaceto)acetate **390** (92 mg, 0.546 mmol) was added to Martin's sulfurane **189** (337 mg, 0.502 mmol) in Et_2O (3 mL) at RT. After 40 min. the solvent was removed under vacuum. The residue was purified through silica gel column

chromatography (50 % AcOEt in pentane) where 2-acetyl-2-(diphenyltiomethylene)-4-(pentylaceto)acetate **301** (159 mg, 90 %) was obtained as a colorless viscous liquid.

R_f = 0.23 (silica, 50% AcOEt in pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79 (p, J = 6.7 Hz, 2H, CHCC*H*$_2$); 1.88 (t, J = 2.7 Hz, 1H, C*H*CCH$_2$); 2.19 (dt, J= 2.7, Hz, J= 7.1Hz, 2H, OCH$_2$C*H*$_2$); 2.41 (s, 3H, C*H*$_3$CO); 4.09 (t, J= 6.3 Hz, 2H, OC*H*$_2$); 7.53-7.52 (m, 4H, *Ph*); 7.46-7.39 (m,6H, *Ph*).

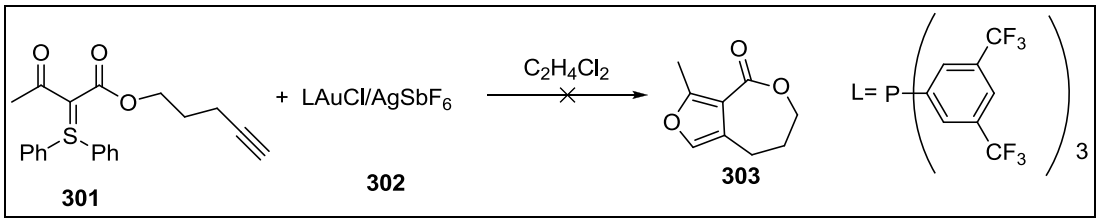
^{13}C NMR (125 MHz, $CDCl_3$): δ 15.44 (CHC*C*H$_2$), 27.92 (OCH$_2$*C*H$_2$), 29.93 (*C*H$_3$CO), 62.09 (O*C*H$_2$), 68.89 (*C*HCCH$_2$), 83.29 (CH*C*CH$_2$), 129.42, 129.51, 129.85, 131.29 (*Ph*), 166.43 (O*C*O), 191.04 (CH$_3$*C*O).

IR (neat, cm^{-1}): 1663, 1588, 1574, 1312, 1057, 742.

MS (EI) *m/z*: 43, 186, 269, 352.

HMRS (EI): *m/z* calcd. $[M]^+$= 375.1025, found $[M]^+$: 375.1028.

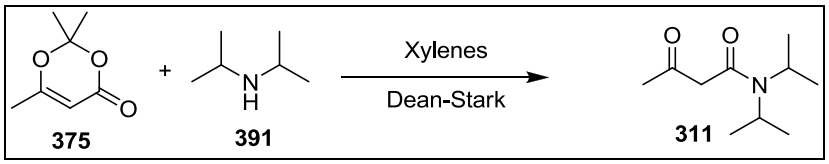
5.6.1.5. Attempt to decompose 2-acetyl-2-(diphenyltiomethylene)-4-(pentylaceto)acetate



Scheme 226

A dry schlenk tube was charged with 2-acetyl-2-(diphenyltiomethylene)-4-(pentylaceto)acetate **301**, (69.2 mg, 0.2 mmol), chloro(tri(trifluoromethyl)phosphine)gold(I) **302'** 95% (9.0 mg, 0.01 mmol) and $AgSbF_6$ **302''**(3.3 mg, 0.01 mmol). The tube was evacuated and back filled with argon, and this procedure was repeated three times. The mixture was dissolved by dry $C_2H_4Cl_2$ (1 mL), then stirred at 60 ºC for 16h. Since no reaction occurred (TLC) it was stirred for 48h under reflux, where no conversion was obtained.

5.6.1.6. **Synthesis of 2-(acetyl)-N-(di*iso*propyl)acetamide.**



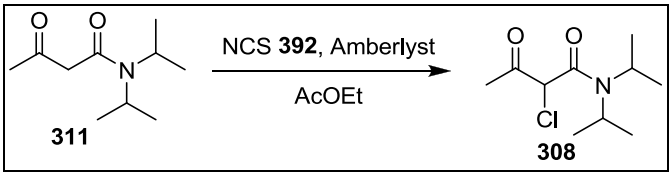
Scheme 227

Prepared following general procedure[132]

In a round bottom flask, diisopropylamine **391** (1.4 mL, 9.9 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (1.3 mL, 9.9 mmol) in xylenes (4.5 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring while adding diisopropylamine (0.3 mL, 2.1 mmol) every hour for 5h. The volatile compounds were removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(di*iso*propyl)acetamide **311** was obtained as a brown liquid (1.7g, 93 %) and as a keto-enol equilibrium mixture (1:0.3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, J= 5.6 Hz, 6H, NCH(C*H*$_3$)$_2$ keto); 1.25 (bs, 6H, NCH(C*H*$_3$)$_2$ enol); 1.33 (bs, 6H, NCH(C*H*$_3$)$_2$ enol); 1.40 (d, J= 6.8 Hz, 6H, NCH(C*H*$_3$)$_2$ keto); 1.94 (s, 3H, C*H*$_3$CO enol); 2.26 (s, 3H, C*H*$_3$CO keto); 3.46-3.49 (m, 3H, NC*H* keto, COC*H*$_2$CO keto overlapped); 3.82 (sp, J= 6.8 Hz, 1H, NC*H* enol); 3.91 (bs, 1H, NC*H* keto); 5.09 (s, 1H, NCOC*H*); 15.30 (s, 1H, CH$_3$CO*H* enol).
^{13}C NMR (100 MHz, $CDCl_3$): δ 20.40 (NCH(*C*H$_3$)$_2$); 20.74 (NCH(*C*H$_3$)$_2$); 22.22 (*C*H$_3$CO enol); 29.96 (*C*H$_3$CO keto); 46.05 (N*C*H); 49.82 (N*C*H); 52.46 (CO*C*H$_2$CO); 165.34 (N*C*O keto); 171.78 (*C*O enol); 174.39 (*C*O enol); 203.17 (CH$_3$*C*O keto).
IR (neat, cm^{-1}): 2970, 1719, 1637, 1340, 1045
MS (EI) *m/z*: 128, 142
HMRS (ESI$^+$): *m/z* calcd. [M]$^+$= 185.141579, found [M]$^+$: 185.141389.

5.6.1.7. **Synthesis of 2-(acetyl)-2-chloro-N-(di*iso*propyl)acetamide**



Scheme 228

2-(acetyl)-N-(di*iso*propyl)acetamide **311** (808 mg, 4.37 mmol) and N-chlorosuccinimide **392** (646 mg, 4.82 mmol) were mixed in AcOEt (11.2 mL) at RT under stirring. Amberlyst was added (966 mg) and the reactional mixture stirred for 35 min. The amberlyst was removed by filtration and the reactional mixture dried with anydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified through silica flash chromatography (15 % AcOEt in hexanes) where the 2-(acetyl)-2-chloro-N-(di*iso*propyl)acetamide **308** (537 mg, 56 %) was isolated as a white solid.

Adapted from reported procedure[136].

m.p.= 61-63 ºC

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20-1.23 (m, 6H, NCH(C*H*$_3$)$_2$); 1.35-1.40 (m, 6H, NCH(C*H*$_3$)$_2$); 2.36 (s, 3H, C*H*$_3$CO); 3.45 (sp, J= 6.9 Hz, 1H, NC*H*); 3.95 (sp, J= 6.6 Hz, 1H, NC*H*); 4.86 (s, 1H, COC*H*ClCO).

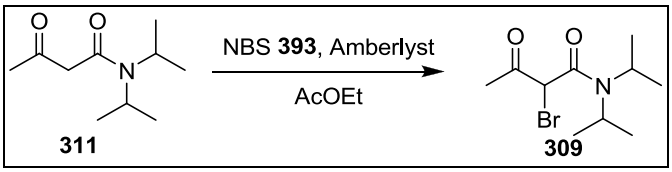
^{13}C NMR (75 MHz, $CDCl_3$): δ 19.87, 20.01, 20.37, 20.73 (NCH(*C*H$_3$)$_2$), 26.77 (*C*H$_3$CO), 46.74 (N*C*H), 49.84 (N*C*H), 61.78 (CO*C*HClCO), 163.64 (N*C*O), 198.84 (CH$_3$*C*O).

IR (neat, cm^{-1}): 2971, 1749, 1646, 1443, 1337, 1043, 767

MS (EI) *m/z*: 85, 97, 196, 219

HMRS (ESI$^+$): *m/z* calcd. [M+Na]$^+$= 242.092067, found [M+Na]$^+$: 242.091823

5.6.1.8. **Synthesis of 2-(acetyl)-2-bromo-N-(di*iso*propyl)acetamide**



Scheme 229

Adapted from reported procedure[136].

2-(acetyl)-N-(di*iso*propyl)acetamide **311** (806 mg, 4.36 mmol) and N-bromosuccinimide **393** (817 mg, 4.58 mmol) were mixed in AcOEt (11.2 mL) at RT under stirring. Amberlyst was added (960 mg) and the reactional mixture stirred for 50 min. The amberlyst was removed by filtration and the reactional mixture dried with anydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified through silica flash chromatography (10 % AcOEt in hexanes) where the 2-(acetyl)-2-bromo-N-(di*iso*propyl)acetamide **309** (601 mg, 50 %) was isolated as a pink solid.

m.p.= 70-73 ºC

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (bs, 6H, NCH(C*H*$_3$)$_2$); 1.35-1.37 (m, 6H, NCH(C*H*$_3$)$_2$); 2.43 (s, 3H, C*H*$_3$CO); 3.42-3.46 (m, 1H, NC*H*); 3.90-3.94 (m, 1H, NC*H*), 4.86 (s, 1H, COC*H*ClCO).

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.76, 20.01, 20.16, 20.76 (NCH(*C*H$_3$)$_2$), 27.08(*C*H$_3$CO), 46.75 (N*C*H), 50.18 (N*C*H), 50.99 (CO*C*HClCO), 163.68 (N*C*O), 198.21 (CH$_3$*C*O).

IR (neat, cm^{-1}): 2971, 1747, 1639, 1444, 1334, 1043

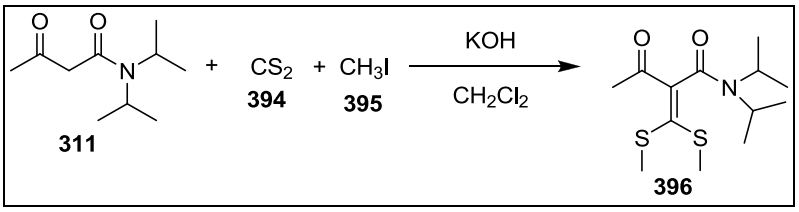
MS (EI) *m/z*: 128, 184, 164, 263

HMRS (ESI$^+$): *m/z* calcd. [M+Na]$^+$= 286.041320, found [M+Na]$^+$: 286.041595

5.6.1.9. General procedure for the α-halogenated acetamides base screening

In a carousel the α-halogenated acetamide **308** or **309** (30 mg) was added to $Rh_2(OAc)_4$ (1 mol %) followed by $C_2H_4Cl_2$ (1 mL) at RT. The base was added (1.1 eq) and the solution was stirred at RT. When the TCL displayed substrate consumption the temperature was maintained otherwise the mixture was refluxed. After the designated time the solvent was removed under reduced pressure and a ^1H NMR taken to determine the conversion. The specific used conditions and observed results are provided on Scheme 134 and Scheme 135.

5.6.1.10. Synthesis of 2-(acetyl)-2-(bis(methylthio)methylene)-N-(di*iso*propyl)acetamide



Scheme 230

Adapted from reported procedure[137].

To a solution of 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (752 mg, 4.07 mmol) in CH_2Cl_2 (42 mL) under vigorous stirring and at RT was added KOH (1.35 g, 25.4 mmol). After 5 min. CS_2 **394** (1.4 mL, 23.3 mmol) was added and the solution turned orange. After 30 min. CH_3I **395** (0.52 mL, 8.4 mmol) was added at 0 ºC. The reaction was allowed to reach RT during the night. On the next day the reaction mixture was filtrated and the solvent evaporated. The residue was purified through silica flash chromatography (20 % AcOEt in hexanes) where 2-(acetyl)-2-(bis(methylthio)methylene)-N-(di*iso*propyl)acetamide **396** (1.00g, 86 %) was obtained as a yellow solid.

R_f = 0.38 (silica, 30% AcOEt in hexanes).

m.p.= 64-66 ºC

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, J= 6.6 Hz, 6H, NCH(CH_3)$_2$); 1.50 (d, J= 6.6 Hz, 6H, NCH(CH_3)$_2$); 2.31, 2.38, 2.43 (s, 3H, 2xSCH_3, CH_3CO); 3.46 (sp, J= 6.6 Hz, 1H, NC*H*); 3.89 (sp, J= 6.6 Hz, 1H, NC*H*).

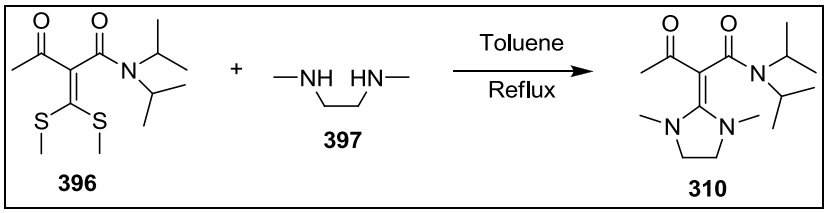
^{13}C NMR (75 MHz, $CDCl_3$): δ 17.20, 18.68 (S*C*H_3), 19.93, 20.72 (NCH(*C*H_3)$_2$), 29.17 (*C*H_3CO), 45.92 (N*C*H), 50.94 (N*C*H), 140.87, 149.65 (CO*CC*S), 165.96 (N*C*O), 194.76(CH$_3$*C*O).

IR (neat, cm^{-1}): 2971, 1626, 1439, 1329, 613.

MS (EI) *m/z*: 43, 100, 189, 242, 246, 289

HMRS (ESI$^+$): *m/z* calcd. [M+Na]$^+$= 312.106242, found [M+Na]$^+$: 312.106341.

5.6.1.11. **Synthesis of 2-(acetyl)-2-(N,N-dimethylimidazolidin-2-ylidene)-N-(di*iso*propyl)acetamide**



Scheme 231

Adapted from reported procedure[112].

A solution of 2-(acetyl)-2-(bis(methylthio)methylene)-N-(di*iso*propyl)acetamide **396** (418 mg, 1.45 mmol) and N,N′-dimethylethylenediamine **397** (0.156 mL, 1.45 mmol) in toluene (14.4 mL) was refluxed for 25h. The solvent was evaporated and the residue crystallized from AcOEt / Hexanes (2x). The 2-(acetyl)-2-(N,N-dimethylimidazolidin-2-ylidene)-N-(di*iso*propyl)acetamide **310** (220 mg, 54 %) was obtained as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (d, J= 4.5 Hz, 12H, N(CH(CH_3)$_2$)$_2$); 2.19 (s, 3H, CH_3CO); 2.94 (s, 6H, NCH_3); 3.65 (bs, 6H, NC*H*, NCH_2CH_2N, overlapped).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (N(CH(*C*H_3)$_2$)$_2$), 27.60 (*C*H_3CO), 36.70 (N*C*H_3), 49.69 (N*C*H_2*C*H_2N), 87.88 (CO*C*CO), 167.75 (N*C*O), 171.06 (N*C*N), 187.6 (CH$_3$*C*O).

MS (EI) *m/z*: 100, 182, 281.

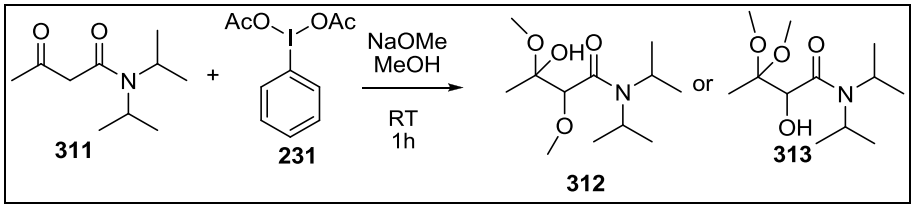
HMRS (ESI^+): *m/z* calcd. $[M+Na]^+$= 304.199546, found $[M+Na]^+$:309.199309.

5.6.1.12. General procedure for the NHC evaluation as diazo surrogate

In a carousel the 2-(acetyl)-2-(N,N-dimethylimidazolidin-2-ylidene)-N-(di*iso*propyl)acetamide **310** (20 mg, 0.071 mmol) was dissolved in $C_2H_4Cl_2$ (1 mL) followed by the catalyst. The mixture was stirred at RT. When the TCL displayed substrate consumption the temperature was maintained otherwise the mixture was refluxed. After the designated time the solvent was removed under reduced pressure and a ^1H NMR taken to determine the conversion. The specific used conditions and observed results are provided on Scheme 137.

5.6.2. Iodine (III)-Mediated Diazo- and Transition Metal-Free C-H Insertion/C-C bond Formation

5.6.2.1. Attempt on synthesizing 2-(acetyl)-2-phenyliodonio-N-(di*iso*propyl)acetamide



Scheme 232

Adapted from reported procedure[116].

To a solution of 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.270 mmol), (diacetoxyiodo)benzene **231** (97 mg, 0.302 mmol), in MeOH (3 mL) was added NaOMe (35 mg, 0.65 mmol). The solution was stirred at cold RT for 1h protected from light. In a dark room and with the glassware cold by a ice/water bath water (6 mL) was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced

pressure, with a ice/water rotavapor bath. The product was dried under high vacuum where the compound **312** or **313** was obtained as a white solid (52 mg, 77 %) with an ambiguous structure. The product is extremely heat sensitive.

The NMR signals were assigned as **312**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.16 (m, 9H, NCH(CH_3)$_2$, CH_3COO overlapped); 1.36 (d, J= 6.8 Hz, 3H, NCHCH_3); 1.41 (d, J= 6.8 Hz, 3H, NCHCH_3); 3.21 (s, 3H, OCH_3); 3.31 (s, 3H, OCH_3); 3.45 (sp, J= 6.8 Hz, 1H, NC*H*); 4.40 (sp, J= 6.8 Hz, 1H, NC*H*); 4.50 (s, 1H, CO*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 17.27 (CH_3COO), 19.79, 19.94, 20.51, 20.75 (NCH(CH_3)$_2$), 46.48, 48.32, 48.52, 48.80 (2x OCH_3, 2x NCH), 68.04 (COO*C*HCO), 102.43 (CH_3*C*OO), 170.57 (N*C*O).

5.6.2.2. General procedure for substrate-reagent ratio screening

To a round bottom flask, was added (diacetoxyiodo)benzene (**231**) followed by THF (2.5 mL). The solution was stirred at RT until no further (diacetoxyiodo)benzene solubilized. The 4Å sieves (300 mg) were added. The flask was placed at 0ºC with an ice/water bath. The base was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in the THF (1 mL).The reaction mixture was stirred protected from light with aluminum foil. After the reaction time H_2O (1mL) was added and the sieves filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^{1}H NMR spectrum taken. The specific used conditions and observed results are provided on Scheme 141.

5.6.2.3. General procedure for screening the effect of reaction time at 0ºC

To a round bottom flask, was added (diacetoxyiodo)benzene **231** (97 mg, 0.301mmol) followed by THF (2.5 mL). The solution was stirred at RT until no further (diacetoxyiodo)benzene solubilized. The 4Å sieves (300 mg) were added. The flask was

placed at 0ºC with an ice/water bath. KO^{t}Bu (82 mg, 0.732mmol) was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in the THF (1 mL).The reaction mixture was stirred at 0ºC, protected from light with aluminum foil. After the specific reaction time H_2O (1mL) was added and the sieves filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^{1}H NMR spectrum taken. The specific used conditions and observed results are provided on Scheme 142.

5.6.2.4. General procedure for the solvent screening.

To a round bottom flaskwas added (diacetoxyiodo)benzene **231**(131 mg, 0.41mmol) followed by solvent (3.8 mL). The solution was stirred at RT until no further (diacetoxyiodo)benzene solubilized. The 4Å sieves were added and it was placed at 0ºC with an ice/water bath. KO^{t}Bu (82 mg, 0.732mmol) was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in the solvent (1 mL).The reaction mixture was stirred protected from light with aluminum foil. After the specific reaction time H_2O (1mL) was added and the sieves filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^{1}H NMR spectrum was taken. The specific used conditions and observed results are provided on Scheme 143.

5.6.2.5. General procedure for screening at low temperatures (-30, -78 ºC)

To a round bottom flaskwas added (diacetoxyiodo)benzene **231** followed by dried THF. The solution was stirred at RT until no further (diacetoxyiodo)benzene solubilized. The 4Å sieves were added and the flask was placed at -30 or -78 ºC. KO^{t}Bu (82 mg, 0.732mmol) was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in THF (1 mL) at -30 or -78 ºC.The reaction mixture was

stirred at that temperature protected from light with aluminum foil. After the specific reaction time H_2O (1mL) was added and the sieves filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^1H NMR spectrum taken. The specific used conditions and observed results are provided on Scheme 144.

5.6.2.6. General procedure for catalytic iodine/co-oxidant screening

To a round bottom flask, was added 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) followed by THF (3.8 mL). The solution was stirred and 4Å sieves were added (200 to 300 mg) and then 3-chloroperbenzoic acid (*m*-CPBA) (186 mg, 1.08 mmol) or *tert*-butyl hydroperoxide (TBHP) in decane (5.5M solution, 0.25 mL, 1.375 mmol, TBHP). The suspension was placed at 0ºC and Cs_2CO_3 (352 mg, 1.08 mmol) was added followed by PhI (15μL, 0.134mmol) and AcOH (7.7μL, 0.123 mmol) or tetrabutylammonium iodide (20 mg, 0.054 mmol, TBAI). After the reaction time H_2O (1mL) was added and the sieves filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^1H NMR spectrum taken. The specific used conditions and observed results are provided on Scheme 145.

5.6.2.7. General procedure for iodine oxidant source screening

To a round bottom flask, was added the iodine oxidant followed by THF (3.8 mL). The solution was stirred at RT until no further iodine reagent solubilized. The 4Å sieves were added and it was placed at 0ºC with an ice/water bath. KO^tBu (82 mg, 0.732mmol) was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in THF (1 mL).The reaction mixture was stirred protected from light with aluminum foil. After the specific reaction time H_2O (1mL) was added and the sieves

filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^1H NMR spectrum was taken. The specific used conditions and observed results are provided on Scheme 146.

5.6.2.8. General procedure for additives effect

To a flame dried round bottom flask, under Argon, was added (diacetoxyiodo) benzene **231** (131 mg, 0.41mmol) followed by THF (3.8 mL). The solution was stirred at RT until no further (diacetoxyiodo)benzene solubilized. The 4Å sieves (200 mg) were added and then the additive. The flask was placed at 0ºC with an ice/water bath. KO^tBu (82 mg, 0.732mmol) was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in the THF (1 mL).The reaction mixture was stirred protected from light with aluminum foil. After the reaction time H_2O (1mL) was added and the sieves filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^1H NMR spectrum taken. The specific used conditions and observed results are provided on Scheme 147.

5.6.2.9. General procedure for bases screening

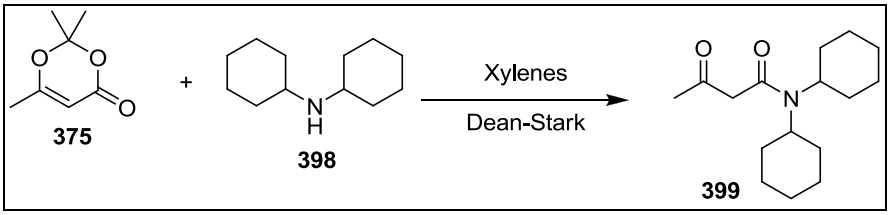
To a round bottom flask was added (diacetoxyiodo)benzene **231** (131 mg, 0.41mmol) followed by dried THF (3.8 mL). The solution was stirred at RT until no further (diacetoxyiodo)benzene solubilized. The 4Å sieves were added and the flask was placed at determined temperature. Base was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in THF (1 mL).The reaction mixture was stirred protected from light with aluminum foil. After the reaction time H_2O (1mL) was added and the sieves filtrated over a celite pad in a Pasteur pipette. The solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4. The solution was filtrated and the solvents removed. 1,3,5-trimethoxybenzene was added as internal standard and a ^1H NMR

spectrum was taken. The specific used conditions and observed results are provided on Scheme 148.

5.6.2.10. General procedure for final reaction temperature screening

To a round bottom flask, was added (diacetoxyiodo)benzene **231** (131 mg, 0.407mmol) followed by THF (3.8 mL). The solution was stirred at RT until no further (diacetoxyiodo)benzene solubilized. The flask was placed at 0ºC with an ice/water bath. NaH (24 mg, 0.600mmol) was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (50 mg, 0.27 mmol) dissolved in the THF (1 mL).The reaction mixture was protected from light with aluminum foil and stirred at 0ºC and then at RT. After the reaction time NH_4Cl aq. sat. (6mL) was added and the solution was extracted 3 times with dichloromethane and the combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated. Purification by column chromatography neutral alumina with 25% AcOEt in hexanes afforded the desired product or 1,3,5-trimethoxybenzene was added as internal standard and a ^1H NMR spectrum taken. The specific used conditions and observed results are provided on Scheme 149.

5.6.2.11. Synthesis of 2-(acetyl)-N-(dicyclohexyl)acetamide



Scheme 233

Prepared following general procedure[132]

In a round bottom flask, dicyclohexylamine **398** (1.0 mL, 5.0 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (606 mg, 4.3 mmol) in xylenes (2 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-

(dicyclohexyl)acetamide **399** was obtained as a brown viscous liquid (1.1g, 96 %) and as a keto-enol equilibrium mixture (1:0.15).

R_f = 0.47 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06-1.79 (m); 1.89 (s, 3H, C*H*$_3$CO enol); 2.21 (s, 3H, C*H*$_3$CO keto); 2.40 (m, 2H); 2.87 (m, 1H); 3.25 (m, 1H); 3.44 (s, 2H, COC*H*$_2$CO); 5.06 (s, 1H, NCOC*H* enol); 15.25 (s, 1H, CH_3CO*H* enol).

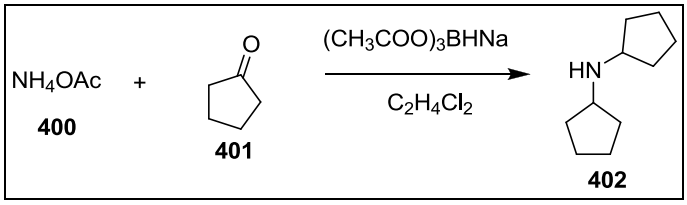
^{13}C NMR (100 MHz, $CDCl_3$): δ 22.19 (*C*H_3CO enol); 25.10, 25.25, 25.62, 25.81, 26.47, 26.93, 29.76 (*C*H_2CH_2); 29.84 (*C*H_3CO keto); 31.11; 52.55 (CO*C*H_2CO); 56.19, 58.91(N*C*H); 165.60 (N*C*O keto); 203.18 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2931, 2855, 1721, 1636, 1453,1362, 1314.

MS (ESI^+) *m/z*: 182, 226

HMRS (ESI^+): *m/z* calcd. $[M+Na]^+$= 288.193397, found $[M+Na]^+$: 288.193550

5.6.2.12. **Synthesis of dicyclopentylamine**



Scheme 234

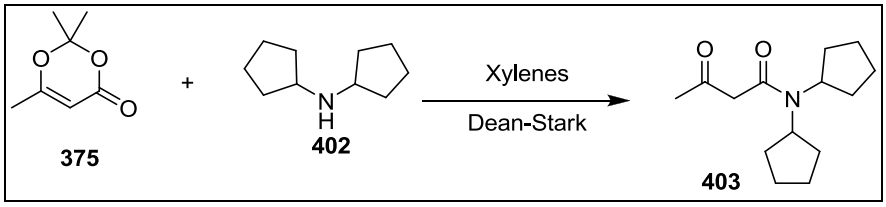
Prepared following general procedure[138]

In a round bottom flask, cyclopentanone **401** (828 mg, 9.8 mmol) and ammonium acetate **400** (6.65 g, 0.086 mol) were mixed in 1,2-dichloroethane (31 mL). Sodium triacetoxyborohydride (2.65g, 12.5 mmol) was added followed by Et_3N (2.5 mL, 17.9 mmol). The reaction was stirred for 64 h at RT turning black. $NaHCO_3$ aq. sat. was added and the mixture was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents evaporated. The residue was purified through silica gel chromatography 50% AcOEt in hexanes and then 10 % Et_3N in hexanes to collect the product. Dicyclopentylamine **402** was obtained as a yellow liquid (460 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22-1.32 (m, 4H, C*H*$_2$); 1.45-1.55 (m, 4H, C*H*$_2$); 1.62-1.70 (m, 4H, C*H*$_2$); 1.82-1.88 (m, 4H, C*H*$_2$); 3.05-3.12 (m, 2H, NC*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.94 (*C*H_2); 33.54 (*C*H_2); 58.54 (N*C*H).

5.6.2.13. Synthesis of 2-(acetyl)-N-(dicyclopentyl)acetamide



Scheme 235

Prepared following general procedure[132]

In a round bottom flask, dicyclopentylamine **402** (300 mg, 1.96 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (277 mg, 1.95 mmol) in xylenes (3.2 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(dicyclopentyl)acetamide **403** was obtained as a yellow liquid (415 mg, 90 %) and as a keto-enol equilibrium mixture (1:0.15).

R_f = 0.31 (silica, 20% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48-1.21 (m; 16H, C*H*$_2$C*H*$_2$; 3H, C*H*$_3$CO enol); 2.24 (s, 3H, C*H*$_3$CO keto); 3.39-3.46 (m, 1H, NC*H*); 3.50 (s, 2H, COC*H*$_2$CO); 3.95-4.01 (m, 1H, NC*H*); 5.08 (s, 1H, NCOC*H* enol); 15.20 (s, 1H, CH_3CO*H* enol).

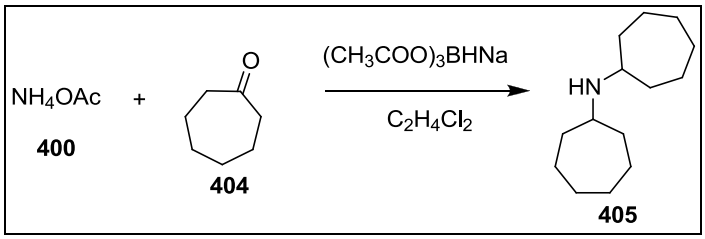
^{13}C NMR (100 MHz, $CDCl_3$): δ 22.17 (*C*H_3CO enol); 24.51(CH_2CH_2); 25.83 (CH_2CH_2); 29.55 (*C*H_3CO keto); 29.91 (CH_2CH_2); 29.98 (CH_2CH_2); 52.54 (CO*C*H_2CO); 56.31 (N*C*H); 59.94 (N*C*H); 88.75 (NCO*C*H enol); 165.18 (N*C*O keto); 171.68 (*C*O enol); 174.16 (*C*O enol); 203.15 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2954, 2869, 1719, 1633, 1350, 1170

MS (EI) *m/z*: 69, 84, 168

HMRS (ESI^+): *m/z* calcd. $[M+Na]^+$= 260.162099, found $[M+Na]^+$: 260.161931

5.6.2.14. Synthesis of dicycloheptylamine



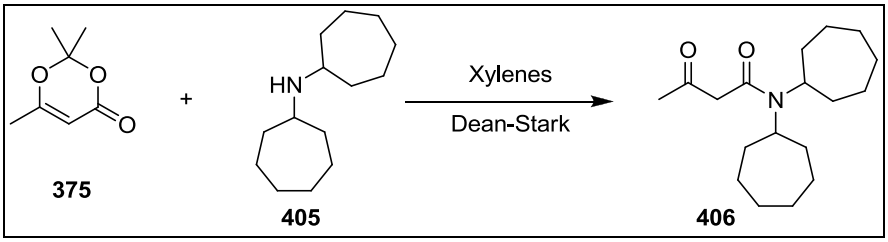
Scheme 236

Prepared following general procedure[138]

In a round bottom flask, cycloheptanone **404** (1.0 g, 8.6 mmol) and ammonium acetate **400** (6.59 g, 0.89 mol) were mixed in 1,2-dichloroethane (31 mL). Sodium triacetoxyborohydride (2.65g, 0.0125mol) was added followed by Et_3N (2.5 mL, 17.9 mmol). The reaction was stirred for 48 h at RT. $NaHCO_3$ aq. sat. was added and the mixture was extracted with AcOEt (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through silica gel chromatography 50% AcOEt in hexanes and then 10 % Et_3N in hexanes to collect the product. Dicycloheptylamine **405** was obtained as a yellow liquid (722 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27-1.66 (m, 20H, C*H*$_2$); 1.76-1.82 (m, 4H, C*H*$_2$); 2.63-2.70 (m, 2H, NC*H*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 24.52 (*C*H$_2$); 28.20 (*C*H$_2$); 35.40 (*C*H$_2$); 55.60 (N*C*H).

5.6.2.15. Synthesis of 2-(acetyl)-N-(dicycloheptyl)acetamide



Scheme 237

Prepared following general procedure[132]

In a round bottom flask, dicycloheptylamine **405** (400 mg, 1.91 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (273 mg, 1.92 mmol) in xylenes (3 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5.5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(dicycloheptyl)acetamide **406** was obtained as a white crystalline solid (498 mg, 89 %) and as a keto-enol equilibrium mixture (1:0.12).

R_f = 0.34 (silica, 20% AcOEt in hexanes).

m.p.= 65-68 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38-1.74 (m, 24H, CH_2CH_2); 1.89 (s, 3H, CH_3CO enol); 2.21 (s, 3H, CH_3CO keto); 2.36-2.39 (m, 2H); 2.99 (m, 1H, NC*H*); 3.42-3.46 (m, 3H, COCH_2CO, NC*H*); 4.99 (s, 1H, NCOC*H* enol); 15.11-15.33 (m, 1H, CH_3CO*H* enol).

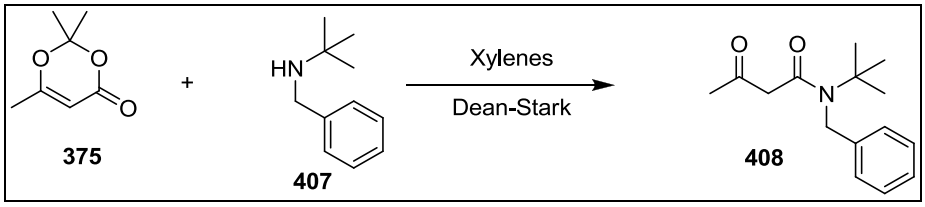
^{13}C NMR (100 MHz, $CDCl_3$): δ 22.20 (*C*H_3CO enol); 25.21, 26.64, 27.26, 28.02 (CH_2*C*H_2); 29.91 (*C*H_3CO keto); 33.01, 33.42 (CH_2*C*H_2); 52.18 (CO*C*H_2CO); 58.26 (N*C*H); 61.36 (N*C*H); 164.52 (N*C*O keto); 203.13 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2925, 2856, 1632, 1486, 1308, 770

MS (EI) *m/z*: 85, 97, 196

HMRS (ESI^+): *m/z* calcd. $[M+Na]^+$= 316.224695, found $[M+Na]^+$: 316.224855

5.6.2.16. Synthesis of 2-(acetyl)-N-(*tert*-butyl)-N-(benzyl)acetamide



Scheme 238

Prepared following general procedure[132]

In a round bottom flask, *N*-benzyl-*tert*-butylamine **407** (853 μL, 4.6 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (567 μL, 4.27 mmol) in xylenes (2 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(*tert*-butyl)-N-(benzyl)acetamide **408** was obtained as a white solid (1.06 g, 99 %) and as a keto-enol equilibrium mixture (1:0.4).

R_f = 0.60 (silica, 30% AcOEt in hexanes).

m.p.= 55-58 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H, NC(C*H*$_3$)); 1.87 (s, 3H, C*H*$_3$CO enol); 2.26 (s, 3H, C*H*$_3$CO keto); 3.47 (s, 2H, COC*H*$_2$CO); 4.59 (s, 2H, PhC*H*$_2$); 4.97 (s, 1H, NCOC*H* enol); 7.22-7.41 (m, 5H, *Ph*); 15.07 (s, 1H, CH_3CO*H* enol).

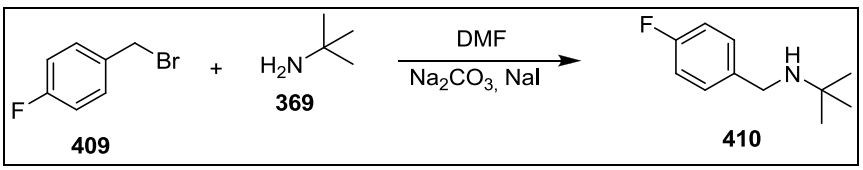
^{13}C NMR (100 MHz, $CDCl_3$): δ 22.10 (*C*H_3CO enol); 28.60 (NC(*C*H_3) keto); 28.95 (NC(*C*H_3) enol); 30.38 (*C*H_3CO keto); 48.85 (Ph*C*H_2 enol); 49.14 (Ph*C*H_2 keto); 52.63 (CO*C*H_2CO); 57.76 (N*C*(CH_3) enol); 58.34 (N*C*(CH_3) keto); 89.91 (NCO*C*H enol); 125.43 (*Ph*); 125.79 (*Ph*); 126.93 (*Ph*); 127.25 (*Ph*);128.72 (*Ph*); 128.94 (*Ph*); 138.73 (*Ph*); 139.30 (*Ph*); 168.38 (N*C*O keto); 174.88 (*C*O enol); 174.95 (*C*O enol); 203.17 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2963, 1635, 1591, 1346, 1240, 707

MS (EI) *m/z*: 57, 91, 190

HMRS (EI): *m/z* calcd. $[M+Na]^+$= 270.146446, found $[M+Na]^+$: 270.146179

5.6.2.17. Synthesis of N-(*tert*-butyl)-N-(*p*-fluorbenzyl)amine



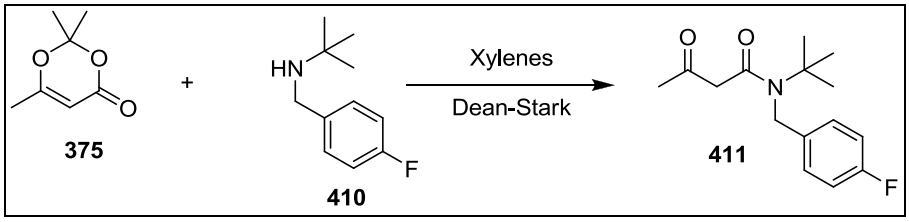
Scheme 239

Adapted from reported procedure[41]

4-Fluorobenzyl bromide **409** (660μL, 5.29 mmol) in DMF (2.1 mL) was added at room temperature during 15 min. period to a solution of *tert*-butylamine **369** (834 μL, 7.93 mmol), sodium carbonate (558 mg, 5.26 mmol), and sodium iodide (65 mg, 0.433 mmol) in DMF (16.6 mL). The reaction mixture was heated at 65 ºC with stirring for 4h and left overnight at room temperature. After the addition of water the mixture was extracted with dichloromethane (3x) and the combined organic layers washed with brine. The mixture was dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. N-(*tert*-butyl)-N-(*p*-fluorbenzyl)amine **410** was distilled at 32ºC, 0.05 mbar and it was obtained as a colorless liquid (0.613 g, 64 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 9H, NC(CH_3)$_3$); 3.70-3.72 (m, 2H, NCH_2); 6.99-7.03 (m, 2H, *Ph*); 7.30-7.34 (m, 2H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 29.13 (NC(CH_3)$_3$); 46.40, 46.50 (NCH_2); 50.56, 50.66 (NC(CH_3)$_3$); 115.11 (d, J_{C-F}= 21 Hz; *C*HCH); 129.72 (d, J_{C-F}= 7.9 Hz; CH*C*H); 137.20 (d, J_{C-F}= 2.7 Hz; CH_2C); 161.79 (d, J_{C-F}= 243 Hz; *C*F).
^{19}F NMR (376 MHz, $CDCl_3$): δ –116.49 (s, C*F*).

5.6.2.18. Synthesis of 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-fluorbenzyl)acetamide



Scheme 240

Prepared following general procedure[132]

In a round bottom flask, the N-(*tert*-butyl)-N-(*p*-fluorbenzyl)amine **410** (494 mg, 2.73 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (348 mg, 2.45 mmol) in xylenes (2 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes,

gradient). 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-fluorbenzyl)acetamide **411** was obtained as a yellow viscous liquid (578 mg, 89%) and as a keto-enol equilibrium mixture (1:0.35).

R_f = 0.42 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43-1.44 (m, 9H, NC(C*H*$_3$)$_3$); 1.84 (s, 3H, C*H*$_3$CO enol); 2.24 (s, 3H, C*H*$_3$CO keto); 3.44 (s, 2H, COC*H*$_2$CO); 4.53 (s, 2H, PhC*H*$_2$); 4.92 (s, 1H, NCOC*H* enol); 7.02-7.19 (m, 4H, C*H*C*H*); 15.03 (s, 1H, CH$_3$CO*H* enol).

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.12 (*C*H$_3$CO enol); 28.57 (NC(*C*H$_3$)$_3$ keto); 28.93 (NC(*C*H$_3$)$_3$ enol); 30.44 (*C*H$_3$CO keto); 48.17 (Ph*C*H$_2$ enol); 48.50 (Ph*C*H$_2$ keto); 52.53 (CO*C*H$_2$CO); 57.76 (N*C*(CH$_3$)$_3$ enol); 58.36 (N*C*(CH$_3$)$_3$ keto); 89.67 (NCO*C*H enol); 115.59 (d, $J_{C\text{-}F}$ = 22 Hz, *C*HCH enol); 115.85 (d, $J_{C\text{-}F}$ = 21 Hz, *C*HCH keto); 127.00 (d, $J_{C\text{-}F}$ = 7 Hz, CH*C*H keto); 127.32 (d, $J_{C\text{-}F}$ = 8 Hz, *C*HCH enol); 134.38 (d, $J_{C\text{-}F}$ = 3 Hz, CH$_2$*C*H keto); 134.91(d, $J_{C\text{-}F}$ = 3 Hz, CH$_2$*C*H keto); 161.79 (d, $J_{C\text{-}F}$ = 243 Hz, C*F* enol); 161.94 (d, $J_{C\text{-}F}$ = 245 Hz, C*F* keto); 168.29 (N*C*O keto); 174.85 (*C*O enol); 175.08 (*C*O enol); 203.11 (CH$_3$*C*O keto).

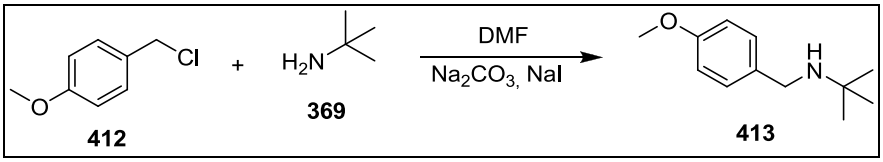
^{19}F NMR (376 MHz, $CDCl_3$): δ –116.00-–115.93 (m, C*F* enol); –115.45-–115.40 (m, C*F* keto)

IR (neat, cm^{-1}): 2967, 1719, 1633, 1511, 1223, 822

MS (EI) *m/z*: 43, 57, 109, 208, 222

HMRS (ESI$^+$): *m/z* calcd. [M+Na]$^+$= 288.137023, found [M+Na]$^+$: 288.136878

5.6.2.19. Synthesis of N-(*tert*-butyl)-N-(*p*-methoxybenzyl)amine



Scheme 241

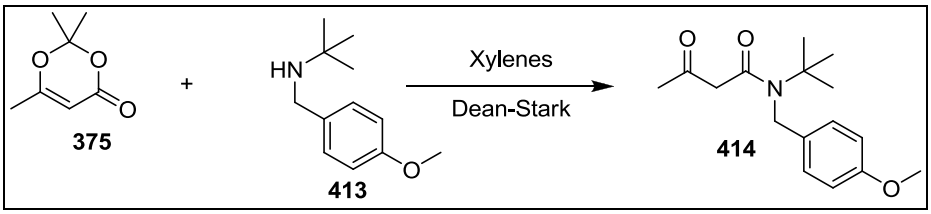
Adapted from reported procedure[41]

4-Methoxybenzyl chloride **412** (720 μL, 5.31 mmol) in DMF (2.1 mL) was added at room temperature during 15 min. period to a solution of *tert*-butylamine **369** (834 μL, 7.93 mmol), sodium carbonate (558 mg, 5.26 mmol), and sodium iodide (65 mg, 0.433

mmol) in DMF (16.6 mL). The reaction mixture was heated at 65 ºC with stirring for 4h and left overnight at room temperature. After the addition of water the mixture was extracted with dichloromethane (3x) and the combined organic layers washed with brine. The mixture was dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. N-(*tert*-butyl)-N-(*p*-methoxybenzyl)amine **413** was distilled at 62 ºC, 0.13 mbar and it was obtained as a colorless liquid (0.584 g, 56 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 9H, NC(CH_3)$_3$); 3.69 (s, 2H, NCH_2); 3.81 (s, 3H, OCH_3); 6.89 (d, J= 3 Hz, 2H, *Ph*); 7.28 (d, J= 2 Hz, 2H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 29.15 (NC(CH_3)$_3$); 46.61 (NCH_2); 50.60 (NC(CH_3)$_3$); 55.28 (OCH_3); 113.81 (CH*C*H); 129.38 (*C*HCH); 133.59 (CH_2C); 158.47 (CH*C*O).

5.6.2.20. **Synthesis of 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-methoxybenzyl)acetamide**



Scheme 242

Prepared following general procedure[132]

In a round bottom flask, N-(*tert*-butyl)-N-(*p*-methoxybenzyl)amine **413** (532 mg, 2.76 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (344 mg, 2.42 mmol) in xylenes (2 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-methoxybenzyl)acetamide **414** was obtained as a colorless viscous liquid (417 mg, 62%) and as a keto-enol equilibrium mixture (1:0.3).

R_f = 0.19 (silica, 20% AcOEt in hexanes).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H, NC(CH_3)$_3$); 1.86 (s, 3H, CH_3CO enol); 2.25 (s, 3H, CH_3CO keto); 3.47 (s, 2H, COCH_2CO); 3.82 (s, 3H, OCH_3); 4.51 (s, 2H,

NC*H*$_2$); 4.98 (s, 1H, NCOC*H* enol); 6.90-6.93 (m, 2H, CHC*H*); 7.12-7.14 (m, 2H, CHC*H*); 15.08 (s, 1H, CH_3CO*H* enol).

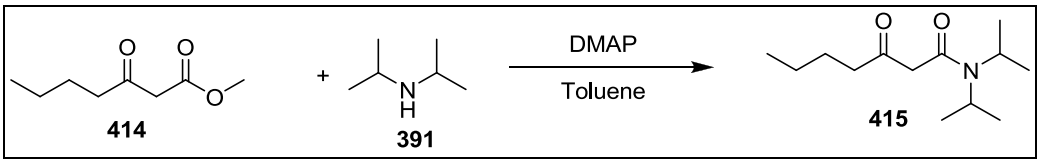
^{13}C NMR (100 MHz, $CDCl_3$): δ 22.11 (*C*H_3CO enol); 28.59 (NC(*C*H_3)$_3$ keto); 28.94 (NC(*C*H_3)$_3$ enol); 30.37 (*C*H_3CO keto); 48.24 (N*C*H_2 enol); 48.58 (N*C*H_2 keto); 52.58 (CO*C*H_2CO); 55.28 (O*C*H_3 enol); 55.31 (O*C*H_3 keto); 57.71 (N*C*(CH_3)$_3$ enol); 58.27 (N*C*(CH_3)$_3$ keto); 89.84 (NCO*C*H enol); 114.11 (CH*C*H enol); 114.33 (CH*C*H keto); 126.54 (*C*HCH keto); 126.89 (*C*HCH enol); 130.52 (NCH$_2$*C* keto); 131.17 (NCH$_2$*C* enol); 158.58 (*C*OCH_3 enol); 158.81 (*C*OCH_3 keto); 168.35 (N*C*O keto); 174.77 (*C*O enol); 174.86 (*C*O enol); 203.20 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2964, 1723, 1633, 1513, 1248, 816.

MS (EI) *m/z*: 121, 136, 162

HMRS (EI): *m/z* calcd. [M]$^+$= 277.1678, found [M]$^+$: 277.1678.

5.6.2.21. Synthesis of N-(di*iso*propyl)-2-(pentanone)acetamide



Scheme 243

In a dry glass pressure tube (Ace pressure tube, Sigma-Aldrich ref.: Z181064) methyl 3-oxoheptanoate **414** (1.0 g, 6.33 mmol), di*iso*propylamine **391** (1.3g, 12.9 mmol) and 4-(dimethylamino)pyridine (255 mg, 2.09 mmol) were added to toluene (13 mL). The tube was closed and the solution was heated and stirred at 130 ºC for 20h. The solvent and the unreacted reagents were evaporated and the residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). N-(di*iso*propyl)-2-(pentanone)acetamide **415** was obtained as a yellow liquid (542 mg, 38%) and as a keto-enol equilibrium mixture (1:0.16).

R$_f$ = 0.22 (silica, 10% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85-0.91 (m, 3H, C*H*$_3$CH$_2$); 1.15 (d, J=6.4 Hz, 6H, NCH(C*H*$_3$)$_2$); 1.24-1.32 (m, 2H, CH_3C*H*$_2$); 1.37 (d, J=6.8 Hz, 6H, NCH(C*H*$_3$)$_2$); 1.51-1.58 (m, 2H, CH_3CH_2C*H*$_2$); 2.12-2.16 (m, 2H, C(OH)C*H*$_2$ enol); 2.53 (t, J= 7.6 Hz, 2H,

COCH_2CH$_2$ keto); 3.41-3.46 (m, 1H, NC*H*); 3.46 (s, 2H, COCH_2CO); 3.77-3.87 (m, 1H, NC*H*); 5.05 (s, 1H, NCOC*H* enol); 15.22 (s, 1H, CH$_2$CO*H* enol).

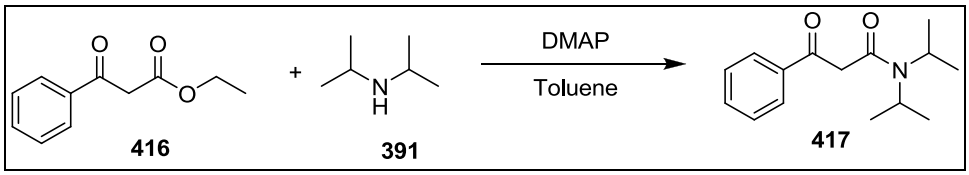
^{13}C NMR (100 MHz, $CDCl_3$): δ 13.80 (*C*H$_3$CH$_2$); 20.38 (NCH(*C*H$_3$)$_2$); 20.70 (NCH(*C*H$_3$)$_2$); 22.16 (CH$_3$*C*H$_2$ keto); 22.32 (CH$_3$*C*H$_2$ enol); 25.58 (CH$_3$CH$_2$*C*H$_2$ keto); 28.72 (CH$_3$CH$_2$*C*H$_2$ enol); 35.87 (C(OH)*C*H$_2$ enol); 42.38 (CO*C*H$_2$CH$_2$ keto); 46.00 (N*C*H); 49.85 (N*C*H); 51.63 (CO*C*H$_2$CO); 165.44 (N*C*O keto); 171.89 (*C*O enol); 177.79 (*C*O enol); 205.32 (CH$_2$CH$_2$*C*O keto).

IR (neat, cm^{-1}): 2964, 1718, 1635, 1337, 1044

MS (EI) *m/z*: 85, 142

HMRS (ESI$^+$): *m/z* calcd. [M+Na]$^+$= 250.177748, found [M+Na]$^+$: 250.177824

5.6.2.22. **Synthesis of 2-(benzoyl)-N-(di*iso*propyl)acetamide**



Scheme 244

In a dry glass pressure tube (Ace pressure tube, Sigma-Aldrich ref.: Z181064) ethyl benzoylacetate **416** (1.0 g, 5.2 mmol) and di*iso*propylamine **391** (1.0 g, 9.9 mmol) were added to toluene (8 mL). The tube was closed and the solution was heated and stirred at 130 ºC for 48h. The solvent and the unreacted reagents were evaporated and the residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(benzoyl)-N-(di*iso*propyl)acetamide **417** was obtained as a brown viscous liquid (415 mg, 32%) and as a keto-enol equilibrium mixture (1:0.4).

R$_f$ = 0.50 (silica, 20% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, J=6.8 Hz, 6H, NCH(C*H$_3$*)$_2$); 1.24-1.39 (m, 6H, NCH(C*H$_3$*)$_2$); 3.39-3.45 (m, 1H, NC*H*); 3.88-3.98 (m, 1H, NC*H*); 4.04 (s, 2H, COCH_2CO); 5.76 (s, 1H, PhCOC*H* enol); 7.38-8.02 (m, 5H, *Ph*); 15.85 (s, 1H, PhCO*H* enol).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.40 (NCH(*C*H$_3$)$_2$); 20.69 (NCH(*C*H$_3$)$_2$); 21.37 (NCH(*C*H$_3$)$_2$); 46.09 (N*C*H); 48.23 (CO*C*H$_2$CO); 50.11 (N*C*H); 86.74 (PhCOC*H* enol);

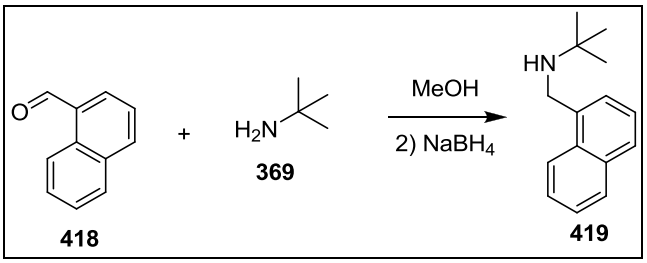
125.80, 128.37, 128.64, 128.65, 130.32, 133.47, 135.57, 136.38 (*Ph*); 165.69 (N*C*O keto); 171.16 (*C*O enol); 171.93 (*C*O enol); 194.50 (Ph*C*O keto).

IR (neat, cm^{-1}): 2969, 1689, 1625, 1574, 1044, 766, 689

MS (EI) *m/z*: 105, 120, 147, 204

HMRS (EI): *m/z* calcd. $[M]^+$= 247.1572, found $[M]^+$: 247.1570.

5.6.2.23. Synthesis of N-(*tert*-butyl)-N-(methyl-1-naphtyl)amine



Scheme 245

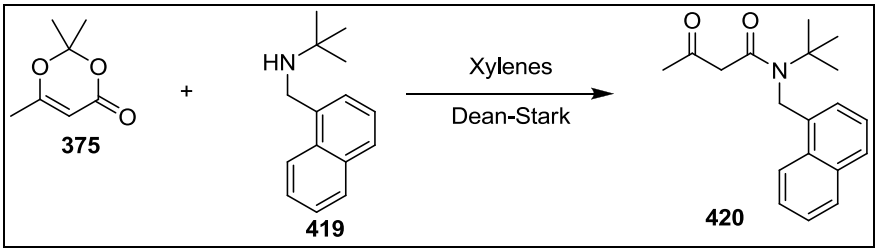
Prepared following general procedure[138]

1-Naphthaldehyde **418** (653 mg, 4.21 mmol) was added to a solution of *tert*-butylamine **369** (326 mg, 4.47 mmol) in MeOH. The solution was stirred at room temperature for 25h and then $NaBH_4$ (254 mg, 6.73 mmol) was carefully added. The solution was stirred for 10 min. NH_4Cl aq. sat. was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). N-(*tert*-butyl)-N-(methyl-1-naphtyl)amine **419** was obtained as a colorless liquid (672 mg, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H, NC(C*H*$_3$)); 4.22 (s, 2H, NC*H*$_2$); 7.44-7.58 (m, 4H, *Naph*); 7.79 (d, J=8.0 Hz, 1H, *Naph*); 7.89 (d, J=8.0 Hz, 1H, *Naph*); 8.19 (d, J=8.4 Hz, 1H, *Naph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.16 (NC(*C*H$_3$)$_3$); 44.80 (N*C*H$_2$); 50.94 (N*C*(CH$_3$)$_3$); 123.79, 125.53, 125.60, 126.01, 126.28, 127.60, 128.70, 131.97, 133.93, 136.96 (*Naph*).

5.6.2.24. **Synthesis of 2-(acetyl)-N-(*tert*-butyl)-N-(methyl-1-naphtyl)acetamide**



Scheme 246

Prepared following general procedure[132]

In a round bottom flask, N-(*tert*-butyl)-N-(methyl-1-naphtyl)amine **419** (400 mg, 1.88 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (269 mg, 1.89 mmol) in xylenes (3 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(*tert*-butyl)-N-(methyl-1-naphtyl)acetamide **420** was obtained as a colorless very viscous liquid (497 mg, 89%) and as a keto-enol equilibrium mixture (1:0.34).

R_f = 0.21 (silica, 20% AcOEt in hexanes).

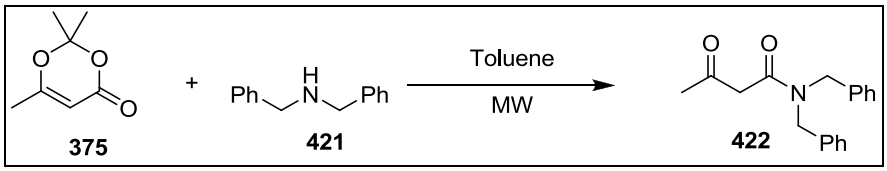
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 9H, NC(C*H*$_3$)); 1.78 (s, 3H, C*H*$_3$CO enol); 2.23 (s, 3H, C*H*$_3$CO keto); 3.43 (s, 2H, COC*H*$_2$CO); 4.85 (s, 1H, NCOC*H* enol); 5.02 (s, 2H, NC*H*$_2$); 7.47-7.60 (m, 4H, *Naph*); 7.81-7.84 (m, 1H, *Naph*); 7.91-7.96 (m, 2H, *Naph*); 15.04 (s, 1H, CH_3CO*H* enol).

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.02 (*C*H_3CO enol); 28.48 (NC(*C*H_3)$_3$ keto); 28.76 (NC(*C*H_3)$_3$ enol); 30.56 (*C*H_3CO keto); 46.89 (N*C*H_2 enol); 46.94 (N*C*H_2 keto); 52.36 (CO*C*H_2CO); 57.77 (N*C*(CH$_3$)$_3$ enol); 58.38 (N*C*(CH$_3$)$_3$ keto); 90.01 (NCO*C*H enol); 121.82, 121.89, 122.82, 123.65, 125.52, 125.70, 125.92, 126.16, 126.35, 126.59, 127.54, 127.89, 129.08, 129.84, 133.64, 133.68, 133.80, 133.91 (*Naph*); 168.76 (N*C*O keto); 174.92 (*C*O enol); 175.25 (*C*O enol); 203.36 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2967, 1723, 1643, 1633, 1395, 1194, 797, 773

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71; O, 10.76. Found: C, 76.47; H, 7.67; N, 4.84; O, 11.02.

5.6.2.25. Synthesis of 2-(acetyl)-N-(dibenzyl)acetamide



Scheme 247

Prepared following general procedure[132]

In a microwave reactor, dibenzylamine **421** (1.2 g, 6.09 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (1.2 mL, 9.04 mmol) in toluene (15 mL). The mixture was heated under microwaves radiation, 120 ºC for 30 min. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(dibenzyl)acetamide **422** was obtained as an orange very viscous liquid (1.52 g, 89%) and as a keto-enol equilibrium mixture (1:0.31).

R_f = 0.35 (silica, 30% AcOEt in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97 (s, 3H, C*H*$_3$CO enol); 2.31 (s, 3H, C*H*$_3$CO keto); 3.66 (s, 2H, COC*H*$_2$CO); 4.44 (s, 2H, PhC*H*$_2$); 4.64-4.66 (m, 2H, PhC*H*$_2$); 5.23 (s, 1H, COC*H*CO enol); 7.17-7.42 (m, 10H, *2Ph*); 14.84 (s, 1H, CH$_3$CO*H* enol).

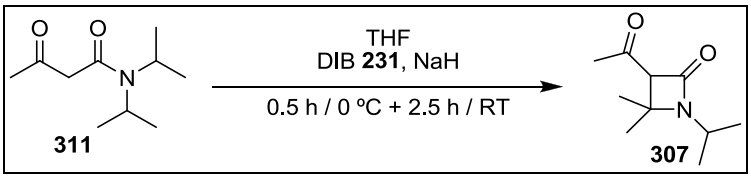
^{13}C NMR (125 MHz, $CDCl_3$): δ 22.12 (*C*H$_3$CO enol); 30.45 (*C*H$_3$CO keto); 47.73, 48.36, 49.68, 49.98, 50.56 (CO*C*H$_2$CO, 2 Ph*C*H$_2$ enol, 2 Ph*C*H$_2$ keto); 86.91 (NCO*C*H enol); 126.38, 126.61, 127.47, 127.56, 127.65, 127.89, 128.09, 128.13, 128.68, 128.72, 128.91, 129.10, 135.94, 136.37, 136.69, 137.18 (2 *Ph*); 167.45 (N*C*O keto); 172.63 (*C*O enol); 175.85 (*C*O enol); 202.41 (CH$_3$*C*O keto).

IR (neat, cm^{-1}): 1723, 1636, 1494, 1452, 700

MS (EI) *m/z*: 43, 91, 190

HMRS (ESI$^+$): *m/z* calcd. [M+Na]$^+$= 304.130799, found [M+Na]$^+$: 304.130486

5.6.2.26. **Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(di*iso*propyl)acetamide**



Scheme 248

Spectral data identical to those reported[132]

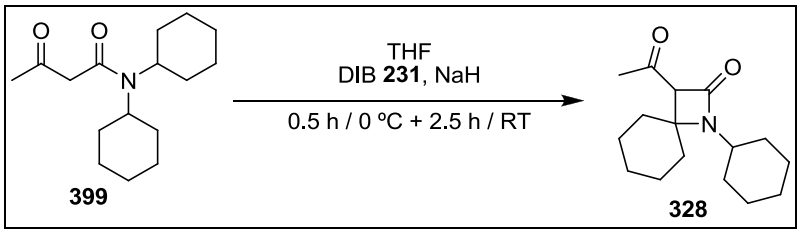
In a round bottom flask was placed (diacetoxyiodo)benzene **231** (131.6 mg, 0.409 mmol), followed by THF (3.8 mL). The solution was stirred until no more (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (25.0 mg, 0.625 mmol) was added followed by 2-(acetyl)-N-(di*iso*propyl)acetamide **311** (49.9 mg, 0.270 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (17 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (25% AcOEt in hexanes) where the 3-(acetyl)-1-*iso*propyl-4,4-dimethyl-β-lactam **307** was isolated as a yellow liquid (33.5 mg, 68%).

R_f = 0.34 (silica, 30 % AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33, 1.35, 1.39, 1.50 (s, 4x 3H, C(C*H*$_3$)$_2$); 2.29 (s, 3H, C*H*$_3$CO); 3.56 (sp, J= 6.8 Hz, 1H, NC*H*); 3.66 (s, 1H, COC*H*CO).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.79, 21.81, 22.90, 27.36 (C(*C*H$_3$)$_2$; 31.05 (*C*H$_3$CO); 44.05 (N*C*H); 59.97 (N*C*CH); 69.80 (CO*C*HCO); 162.39 (N*C*O); 202.34 (CH$_3$*C*O).

5.6.2.27. **Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(dicyclohexyl)acetamide**



Scheme 249

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (131.7 mg, 0.409 mmol), followed by THF (3.8 mL). The solution was stirred until no more (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.4 mg, 0.610 mmol) was added followed by 2-(acetyl)-N-(dicyclohexyl)acetamide **399** (70.1 mg, 0.264 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (20 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (15% AcOEt in hexanes) where 3-acetyl-1-cyclohexyl-1-azaspiro[3.5]nonan-2-one **328**[40] was isolated as a white solid (52.5 mg, 75%).

R_f = 0.40 (silica, 30% AcOEt in hexanes).

m. p.= 71-75 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12-1.78, 2.01-2.05 (m, 20H, CH_2CH_2); 2.29 (s, 3H, CH_3CO); 2.97-3.05 (m, 1H, NC*H*); 3.64 (s, 1H, COC*H*CO).

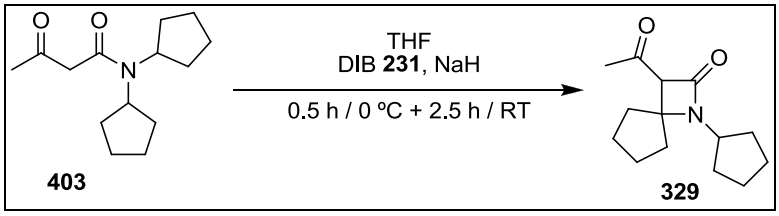
^{13}C NMR (100 MHz, $CDCl_3$): δ 23.66, 24.45, 24.68, 25.04, 25.75, 30.91 (*C*H_2*C*H_2); 31.94 (*C*H_3CO); 32.15, 32.31, 37.90 (*C*H_2*C*H_2); 52.21 (N*C*H); 64.04 (N*C*CHCO); 69.06 (CO*C*HCO); 162.65 (N*C*O); 202.46 (CH$_3$*C*O).

IR (neat, cm^{-1}): 2932, 2855, 1743, 1705, 1452, 1357

MS (EI) *m/z*: 43, 138, 220

HMRS (EI): *m/z* calcd. $[M+Na]^+$= 286.177745, found $[M+Na]^+$: 286.177447

5.6.2.28. **Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(dicyclopentyl)acetamide**



Scheme 250

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (174.3 mg, 0.541 mmol), followed by THF (3.8 mL). The solution was stirred until no more (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.5 mg, 0.613 mmol) was added followed by 2-(acetyl)-N-(dicyclopentyl)acetamide **403** (63.7 mg, 0.268 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (20 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (15% AcOEt in hexanes) providing 3-acetyl-1-cyclopentyl-1-azaspiro[3.4]octan-2-one **329** as a yellow liquid (35.4 mg, 56%).

R_f = 0.31 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51-2.02 (m, 16H, CH_2CH_2); 2.28 (s, 3H, CH_3CO); 3.38 (qt, J= 8.0 Hz, 1H, NC*H*); 3.72 (s, 1H, COC*H*CO).

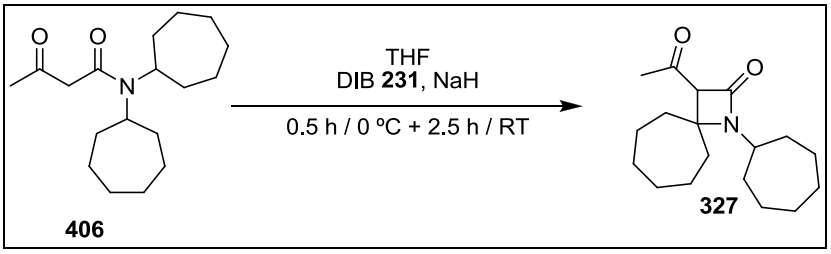
^{13}C NMR (100 MHz, $CDCl_3$): 23.54, 23.81, 24.125, 24.32, 30.07 (*C*H_2*C*H_2); 30.96 (*C*H_3CO); 31.41, 31.60, 36.59 (*C*H_2*C*H_2); 54.04 (N*C*H); 69.20 (N*C*CHCO); 70.32 (CO*C*HCO); 162.74 (N*C*O); 202.95 (CH_3*C*O).

IR (neat, cm^{-1}): 2957, 2872, 1739, 1735, 1356, 949

MS (EI) *m/z*: 43, 124, 192

HMRS (ESI^+): *m/z* calcd. $[M+Na]^+$= 258.146450, found $[M+Na]^+$: 258.146374

5.6.2.29. **Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(dicycloheptyl)acetamide**



Scheme 251

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (174.1 mg, 0.541 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.9 mg, 0.623 mmol) was added followed by 2-(acetyl)-N-(dicycloheptyl)acetamide **406** (79.4 mg, 0.271mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (20 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (15% AcOEt in hexanes) providing 3-acetyl-1-cycloheptyl-1-azaspiro[3.6]decan-2-one **327** as a yellow solid (53.7 mg, 68%).

R_f = 0.20 (silica, 20% AcOEt in hexanes).

m. p.= 62-66 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33-2.07 (m, 24H, CH_2CH_2); 2.29 (s, 3H, CH_3CO); 3.13-3.21 (m, 1H, NC*H*); 3.62 (s, 1H, COC*H*CO).

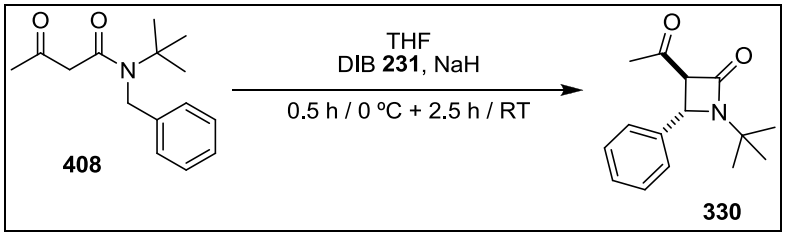
^{13}C NMR (100 MHz, $CDCl_3$): 22.83, 22.89, 24.98, 27.68, 27.69, 28.80, 28.96 (*C*H_2*C*H_2); 31.58 (*C*H_3CO); 34.44, 34.56, 34.82, 39.40 (*C*H_2*C*H_2); 55.24 (N*C*H); 64.77 (N*C*CHCO); 70.13 (CO*C*HCO); 162.28 (N*C*O); 202.82 (CH_3*C*O).

IR (neat, cm^{-1}): 2927, 2856, 1743, 1707, 1357

MS (EI) *m/z*: 43, 152, 248

HMRS (ESI^+): *m/z* calcd. $[M+Na]^+$= 314.209048, found $[M+Na]^+$: 314.208857

5.6.2.30. **Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(*tert*-butyl)-N-(benzyl)acetamide**



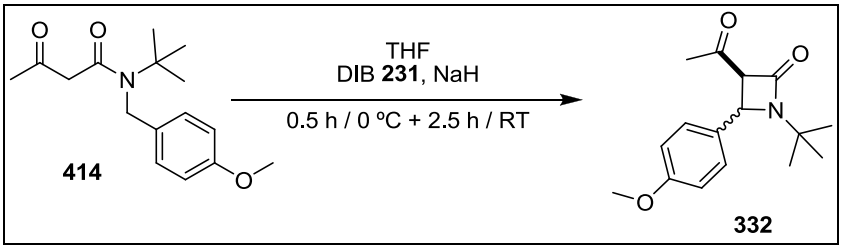
Scheme 252

Spectral data obtained as previously reported[139]

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (174.0 mg, 0.540 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (25.0 mg, 0.625 mmol) was added followed by 2-(acetyl)-N-(*tert*-butyl)-N-(benzyl)acetamide **408** (66.8 mg, 0.270 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (25 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (5 % AcOEt in hexanes) where *trans*-3-(acetyl)-1-(*tert*-butyl)-4-phenyl-β-lactam **330** was isolated as a brown solid (29.9 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 9H, NC(CH_3)$_3$); 2.30 (s, 3H, CH_3CO); 3.93 (d, J= 2.0 Hz, 1H, COC*H*CO); 5.03 (d, J= 1.6Hz, 1H, NC*H*); 7.25-7.42 (m, 5H, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): 28.11 (NC(CH_3)$_3$); 30.09 (CH_3CO); 54.44 (NCH); 55.13 (NC(CH_3)$_3$); 70.86 (COCHCO); 126.64, 128.56, 128.94, 139.32 (*Ph*); 163.03 (NCO); 199.81 (CH_3CO).

5.6.2.31. **Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-methoxybenzyl)acetamide**



Scheme 253

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (175.7 mg, 0.540 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (26 mg, 0.650 mmol) was added followed by 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-methoxybenzyl)acetamide **414** (76 mg, 0.274 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (25 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (10 % AcOEt in hexanes) where *cis* and *trans*-3-(acetyl)-1-(*tert*-butyl)-4-(*p*-methoxyphenyl)-β-lactam **332** were isolated as a yellow liquid mixture (27 mg, 36%) in a 0.20 :1 *cis/trans* ratio.

R_f = 0.40 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 9H, NC(CH_3)$_3$ *trans*); 1.46 (s, 9H, NC(CH_3)$_3$ *cis*); 2.29 (s, 3H, CH_3CO *trans*); 2.39 (s, 3H, CH_3CO *cis*); 3.82 (s, 3H, OCH_3); 3.90 (d, J=1.6 Hz, 1H, COC*H*CO *trans*); 4.67 (d, J= 3.2 Hz, 1H , COC*H*CO or NC*H cis*); 4.73 (s, 1H, NC*H* or COC*H*CO *cis*); 4.98 (d, J=1.6 Hz, 1H, NC*H trans*); 6.90 (d, J= 8.4 Hz, 2H, *Ph tans*); 6.95 (d, J= 8.8 Hz, 2H, *Ph cis*); 7.19 (d, J= 8.4 Hz, 2H, *Ph cis*); 7.32 (d, J= 8.4 Hz, 2H, *Ph trans*).

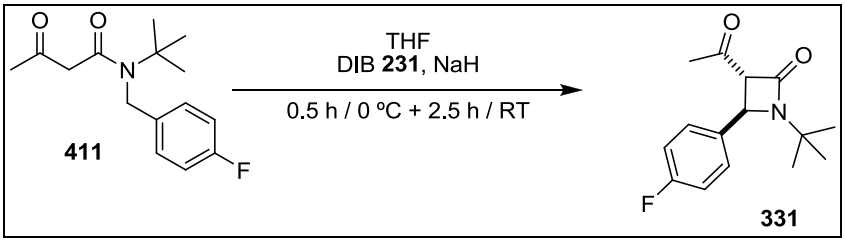
^{13}C NMR (100 MHz, $CDCl_3$): 27.12 (CH_3CO *cis*); 28.11 (NC(CH_3)$_3$ *trans*); 28.22 (NC(CH_3)$_3$ *cis*); 30.04 (CH_3CO *trans*); 48.13 (COCHCO or NCH *cis*); 54.10 (NCH *trans*); 55.03 (NC(CH$_3$)$_3$ *trans*); 55.31 (OCH_3); 59.08 (NC(CH$_3$)$_3$ *cis*); 61.36 (NCH or

CO*C*HCO *cis*); 70.87 (CO*C*HCO *trans*); 114.28 (*Ph trans*); 114.52 (*Ph cis*); 126.58 (*Ph cis*); 127.90 (*Ph trans*); 129.81 (*Ph cis*); 131.10 (*Ph trans*); 159.04 (N*C*O or *Ph cis*); 159.77 (N*C*O or *Ph trans*); 163.04 (*Ph* or N*C*O *trans*); 166.77 (*Ph* or N*C*O *cis*); 199.37 (CH_3*C*O *cis*); 199.95 (CH_3*C*O *trans*).

IR (neat, cm^{-1}): 2975, 1747, 1712, 1515, 1248, 1033, 840

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09; O, 17.43. Found: C, 69.62; H, 7.64; N, 4.65; O, 18.09.

5.6.2.32. Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-fluorbenzyl)acetamide



Scheme 254

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (175.1 mg, 0.544 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.4 mg, 0.610 mmol) was added followed by 2-(acetyl)-N-(*tert*-butyl)-N-(*p*-fluorbenzyl)acetamide **411** (71.9 mg, 0.271mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (25 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (30% AcOEt in hexanes) where *trans*-3-(acetyl)-1-(*tert*-butyl)-4-(*p*-fuorophenyl)-β-lactam **331** was isolated as a white solid (32.4 mg, 45%).

R_f = 0.56 (silica, 30% AcOEt in hexanes).

m. p.= 64-69 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 9H, NC(CH_3)$_3$); 2.30 (s, 3H, CH_3CO); 3.89 (d, J= 2.0 Hz, 1H, COC*H*CO); 5.03 (d, J= 2.0 Hz, 1H, NC*H*); 7.05-7.10 (m, 2H, *Ph*); 7.37-7.41 (m, 2H, *Ph*)

^{13}C NMR (100 MHz, $CDCl_3$): 28.11(NC(CH_3)$_3$); 30.03(CH_3CO); 53.73 (NCH); 55.20 (NC(CH_3)$_3$); 70.97 (COCHCO); 115.95 (d, J_{C-F}= 22 Hz, *Ph*); 128.33 (d, J_{C-F}= 9 Hz, *Ph*); 135.16 (d, J_{C-F}= 3 Hz, *Ph*); 162.70 (d, J_{C-F}= 246 Hz, *C*-F); 162.93 (NCO); 199.63 (CH_3CO).

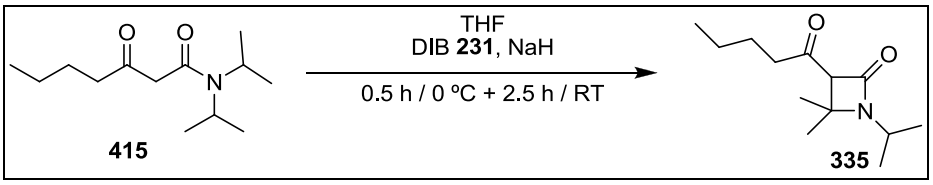
^{19}F NMR (376 MHz, $CDCl_3$): δ –113.04 (C*F*)

IR (neat, cm^{-1}): 2977, 1749, 1712, 1512, 1226, 844

MS (EI) *m/z*: 43, 138, 220

HMRS (EI): *m/z* calcd. $[M+Na]^+$= 286.177745, found $[M+Na]^+$: 286.177447

5.6.2.33. Iodine (III)-mediated C-H insertion on N-(di*iso*propyl)-2-(pentanone)acetamide



Scheme 255

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (174.7 mg, 0.543 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.4 mg, 0.610 mmol) was added followed by N-(di*iso*propyl)-2-(pentanone)acetamide **415** (61.8 mg, 0.272mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (20 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (10% AcOEt in hexanes) where 1-isopropyl-4,4-dimethyl-3-(pentanone)-β-lactam **335** was isolated as a colorless liquid (37.8 mg, 61%).

R_f = 0.54 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J= 7.2 Hz, C*H*$_3$CH$_2$); 1.28-1.34 (m, 11H, NCH(C*H*$_3$)$_2$, NCC*H*$_3$, CH$_3$C*H*$_2$); 1.47 (s, 3H, NCC*H*$_3$), 1.54 (qt, J= 7.2 Hz, 2H, CH$_2$CH$_2$C*H*$_2$); 2.49-2.63 (m, 2H, COC*H*$_2$); 3.54 (sp, J= 6.8 Hz, 1H NC*H*); 3.64 (s, 1H, COC*H*CO).

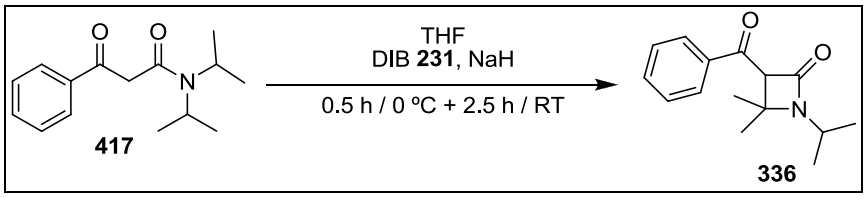
^{13}C NMR (100 MHz, $CDCl_3$): 13.84 (*C*H$_3$CH$_2$); 21.75, 21.77 (NCH(*C*H$_3$)$_2$); 22.14 (CH$_3$*C*H$_2$); 22.84 (NC*C*H$_3$); 24.96 (CH$_2$CH$_2$*C*H$_2$); 27.40 (NC*C*H$_3$); 43.53 (CO*C*H$_2$); 44.43 (N*C*H); 59.89 (N*C*CH); 69.27 (CO*C*HCO); 162.43 (N*C*O); 204.41 (CH$_3$*C*O).

IR (neat, cm^{-1}): 2965, 2934, 2874, 1742, 1709, 1373

MS (EI$^+$) *m/z*: 83, 98, 210

HMRS (ESI$^+$): *m/z* calcd. [M+Na]$^+$= 248.162096, found [M+Na]$^+$: 248.161875

5.6.2.34. **Iodine (III)-mediated C-H insertion on 2-(benzoyl)-N-(di*iso*propyl)acetamide**



Scheme 256

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (131.4 mg, 0.408 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.9 mg, 0.623 mmol) was added followed by 2-(benzoyl)-N-(di*iso*propyl)acetamide **417** (67.1 mg, 0.271mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (27 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (20% AcOEt in hexanes) where 3-

(benzoyl)-1-isopropyl-4,4-dimethyl-β-lactam **336** was isolated as a white solid (41.1 mg, 62%).

R_f = 0.36 (silica, 40% AcOEt in hexanes).

m. p.= 96-99 ºC

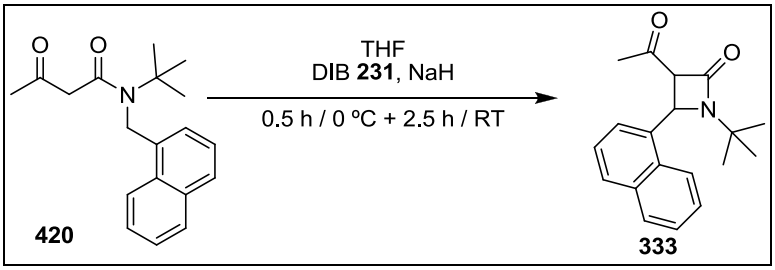
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H, NCC*H*$_3$); 1.35 (d, J= 1.2 Hz, 3H, NCHC*H*$_3$); 1.37 (d, J= 1.2 Hz, 3H, NCHC*H*$_3$); 1.65 (s, 3H, NCC*H*$_3$); 3.60 (sp, J= 6.8 Hz, 1H NC*H*); 4.58 (s, 1H, COC*H*CO); 7.47 (t, J= 7.2 Hz, 2H, *Ph*); 7.58 (t, J= 7.2 Hz, 1H, *Ph*); 7.88 (d, J= 7.2 Hz, 2H, *Ph*);

^{13}C NMR (100 MHz, $CDCl_3$): 21.83, 21.85, 22.04, 27.20 (NC(*C*H$_3$)$_2$, NCH(*C*H$_3$)$_2$); 44.54 (N*C*H); 59.75 (N*C*CH); 66.22 (CO*C*HCO); 128.28, 128.83, 133.63, 136.88 (*Ph*); 162.14 (N*C*O); 193.96 (CH$_3$*C*O).

IR (neat, cm^{-1}): 2976, 1734, 1669, 1333, 1213, 744, 700, 668

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71; O, 13.04. Found: C, 73.17; H, 7.75; N, 5.72; O, 13.36.

5.6.2.35. Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(*tert*-butyl)-N-(methyl-1-naphtyl)acetamide



Scheme 257

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (175.5 mg, 0.545 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.9 mg, 0.623 mmol) was added followed by 2-(acetyl)-N-(*tert*-butyl)-N-(methyl-1-naphtyl)acetamide **420** (80.3 mg, 0.272mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (25 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with

dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (10% AcOEt in hexanes) where *trans*-3-(acetyl)-1-(*tert*-butyl)-4-(1-naphtyl)-β-lactam **333** was isolated as a white solid (32.8 mg, 41%).

R_f = 0.54 (silica, 20% AcOEt in hexanes).

m. p.= 100-104 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H, NC(CH_3)$_3$); 2.32 (s, 3H, CH_3CO); 3.87 (s, 1H, COC*H*CO); 5.98 (s, 1H, NC*H*); 7.50-7.60 (m, 3H, *Naph*); 7.74 (d, J= 8.0 Hz, 1H, *Naph*); 7.90 (d, J= 7.6 Hz, 1H, *Naph*); 8.19 (d, J= 8.0 Hz, 1H, *Naph*).

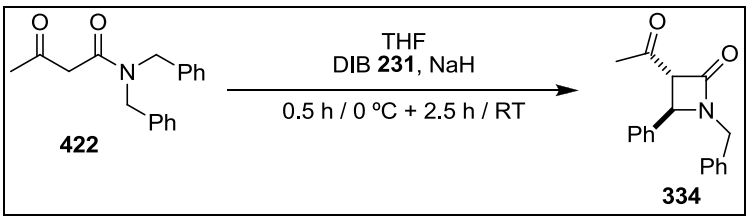
^{13}C NMR (100 MHz, $CDCl_3$): 28.03 (NC(CH_3)$_3$); 30.11 (CH_3CO); 50.15 (N*C*H); 55.13 (N*C*(CH_3)$_3$); 71.40 (CO*C*HCO); 122.46, 122.59, 125.29, 126.19, 126.85, 128.53, 128.90, 130.39, 133.68, 135.52 (*Naph*); 163.80 (N*C*O); 200.05 (CH_3*C*O).

IR (neat, cm^{-1}): 2974, 1750, 1709, 1368, 1166, 783, 774

MS (EI) *m/z*: 153, 195, 223, 238

HMRS (EI): *m/z* calcd. $[M]^+$= 295.1572, found $[M]^+$: 295.1572.

5.6.2.36. Iodine (III)-mediated C-H insertion on N-(dibenzyl)-2-(acetyl)acetamide



Scheme 258

Spectral data obtained as previously reported[140]

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (131.8 mg, 0.409 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.8 mg, 0.620 mmol) was added followed by N-(dibenzyl)-2-(acetyl)acetamide **422** (75.2 mg, 0.268 mmol) dissolved in THF (1mL). The flask was

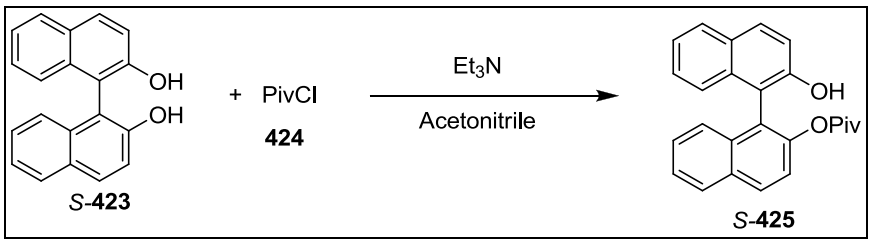
protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (5% AcOEt in hexanes) where *trans*-3-(acetyl)-1-(benzyl)-4-phenyl-β-lactam **334** was isolated as a light brown liquid (30.4 mg, 41%).

R_f = 0.49 (silica, 5% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H, C*H*$_3$CO); 3.86 (d, J= 15.2 Hz, 1H, PhCH*H*); 4.12 (bs, 1H, COC*H*CO); 4.81 (d, J= 15.2 Hz, 1H, PhC*H*H); 4.88 (d, J=1.6 Hz, 1H, NC*H*Ph); 7.26-7.41 (m, 10H, *2Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): 29.99 (*C*H$_3$CO); 44.88 (N*C*H$_2$); 55.19 (N*C*HPh); 71.85 (COC*H*CO); 126.77, 127.89, 128.29, 128.84, 129.12, 134.74, 136.25 (*2Ph*); 163.27 (N*C*O); 199.57 (CH$_3$*C*O).

5.6.2.37. Synthesis of (*S*)-(1,1'-binaphthalene)-2-ol-2'-pivaloyl



Scheme 259

Prepared following reported procedure and spectra data identical to those reported[141].

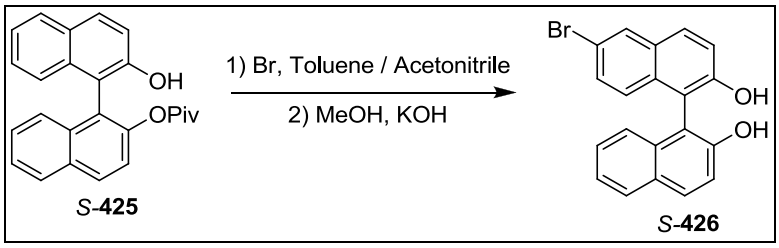
To a solution of (*S*)-1,1'-bi(2-naphthol) *S*-**423** (1.00 g, 3.50 mmol) and Et$_3$N (1.5 mL, 10.8 mmol) in acetonitrile (17 mL) was added pivaloyl chloride **424** (440 μL, 3.58 mmol) dropwise at 0 ºC. The mixture was then allowed to warm to room temperature and stirred for 5h. The reaction mixture was diluted with Et_2O and washed with aqueous HCl (1N, 30 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified through silica flash

chromatography (20 % AcOEt in hexanes) where (*S*)-(1,1'-binaphthalene)-2-ol-2'-pivaloyl *S*-**425** (869 mg, 67 %) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (s, 9H, C(C*H*$_3$)$_3$); 5.24 (s, 1H, O*H*); 7.20 (d, J= 8.4 Hz, 1H, *Naph*); 7.27-7.43 (m, 6H, *Naph*); 7.52-7.56 (m, 1H, *Naph*); 7.87 (d, J=8.0 Hz, 1H, *Naph*); 7.92 (d, J= 8.8 Hz, 1H, *Naph*); 8.00 (d, J=8.0 Hz, 1H, *Naph*); 8.10 (d, J= 8.8 Hz, 1H, *Naph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.47 (C(*C*H$_3$)$_3$), 38.75 (*C*(CH$_3$)$_3$), 114.24, 118.24, 121.82, 123.02, 123.51, 124.57, 125.63, 126.20, 126.65, 127.43, 127.90, 128.32, 129.01, 130.28, 130.70, 132.19, 133.49, 133.64, 148.31, 151.78(*Naph*), 177.82 (*C*OO).

5.6.2.38. Synthesis of (*S*)-(1,1'-binaphthalene)-6-bromo-2,2'-diol



Scheme 260

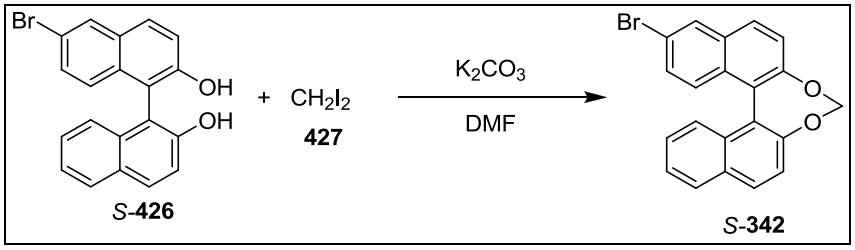
Prepared following reported procedure and spectra data identical to those reported[141].

To a solution of (*S*)-(1,1'-binaphthalene)-2-ol-2'-pivaloyl *S*-**425** (851 mg, 2.3 mmol) in acetonitrile (8.5 mL) and toluene (8.5 mL) at 0 ºC was slowly added bromine (236 μL, 4.6 mmol). The reaction mixture was stirred at 0 ºC for 3h and quenched with aqueous $NaHSO_3$ (3 N, 10 mL). After addition of 16 mL of Et_2O, the organic phase was separated and concentrated to dryness. To this residue were added MeOH (5 mL) and KOH (5 N, 5 mL). The resulting mixture was stirred at room temperature for 2h and was then acidified with 3 N HCl to pH = 1. After addition of AcOEt (40 mL), the organic phase was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. The residue was purified through silica automatic flash chromatography (gradient) where (*S*)-(1,1'-binaphthalene)-6-bromo-2,2'-diol *S*-**426** (827 mg, 98 %) was obtained as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (bs, 2H, O*H*); 7.03 (d, J=9.2 Hz, 1H, *Naph*); 7.11 (d, J=8.4 Hz, 1H, *Naph*); 7.28-7.41 (m, 5H, *Naph*); 7.86 (d, J= 9.2 Hz, *Naph*); 7.86 (d, J= 9.2 Hz, 1H, *Naph*); 7.90 (d, J= 8.0 Hz, 1H, *Naph*); 7.96 (d, J= 8.8 Hz, 1H, *Naph*); 8.05 (d, J= 1.6 Hz, 1H, *Naph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 110.48, 111.58, 117.77, 117.86, 118.99, 124.07, 124.11, 126.20, 127.57, 128.44, 129.39, 130.25, 130.30, 130.51, 130.58, 131.52, 132.12, 133.38, 152.75, 153.00, 171.41 (*Naph*).

5.6.2.39. Synthesis of (*S*)-(1,1'-binaphthalene)-6-bromo-2,2'-dioxepine



Scheme 261

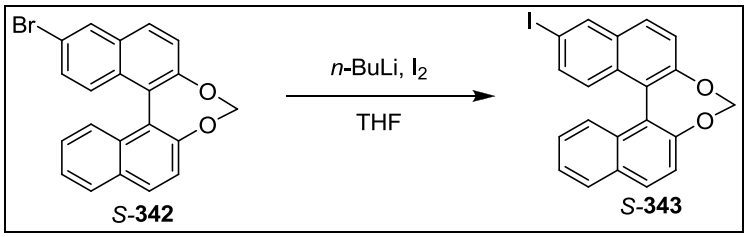
Prepared following reported procedure and spectra data identical to those reported[141].

A mixture of (*S*)-(1,1'-binaphthalene)-6-bromo-2,2'-diol *S*-**426** (535 mg, 1.47 mmol), diiodomethane (355 mL, 4.4 mmol) and anhydrous K_2CO_3 (2.1 g, 151 mmol) in DMF (14.6 mL) was stirred overnight at 80 ºC. After cooling to room temperature, the reaction mixture was poured into water and extracted with AcOEt (30 mL × 2). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. To remove the DMF traces the residue was dissolved in Et_2O and water was added. The water phase was extracted with Et_2O (2x) dried over Na_2SO_4 and concentrated. The residue was purified through silica automatic flash chromatography (gradient) where (*S*)-(1,1'-binaphthalene)-6-bromo-2,2'-dioxepine *S*-**342** (447 mg, 80 %) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (s, 2H, OCH_2O); 7.36-7.56 (m, 7H, *Naph*);7.91 (d, J= 8.8 Hz, 1H, *Naph*); 8.00 (d, J= 8.0 Hz, 1H, *Naph*); 8.04 (d, J= 8.8 Hz, 1H, *Naph*); 8.16 (s, 1H, *Naph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 103.24 (O*C*H_2O); 119.14, 121.02, 123.32, 125.22, 125.60, 126.40, 126.56, 126.61, 128.60, 128.77, 129.40, 129.43, 129.70, 130.39, 130.72, 130.75, 131.88, 132.02, 132.97, 151.46, 151.57 (*Naph*).

5.6.2.40. Synthesis of (*S*)-(1,1'-binaphthalene)-2,2'-dioxepine-6-iodo



S-**342** *S*-**343**

Scheme 262

Adapted from reported procedure[142].

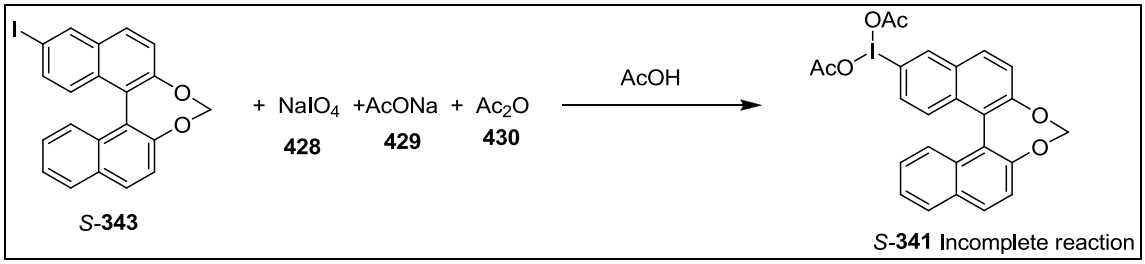
To a solution of (*S*)-(1,1'-binaphthalene)-6-bromo-2,2'-dioxepine *S*-**342** (482 mg, 1.23 mmol) in THF (10 mL) was added a hexane solution of *n*-BuLi (0.84 mL, 2.1 mmol) at -93 °C. The reaction mixture was stirred for 30 min, and then a solution of iodine (524 mg, 1.68 mmol) in THF (1.5 mL) was added. The reaction mixture was allowed to warm to room temperature overnight and was quenched with water. The resulting mixture was treated with aqueous 10% $NaHSO_3$ to destroy excess iodine. After being stirred for 1 h, the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine and dried over Na_2SO_4. The residue was purified through silica preparative TCL (3 x 3 elutions each, 30% toluene in hexanes), where (*S*)-(1,1'-binaphthalene)-2,2'-dioxepine-6-iodo *S*-**343** (441 mg, 85 %) was obtained with 7 % (^{1}H NMR) of (1,1'-binaphthalene)-2,2'-dioxepine as impurity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (s, 2H, OCH_2O); 7.24-7.37 (m, 2H, *Naph*); 7.46-7.55 (m, 5H, *Naph*); 7.88 (d, J= 8.8 Hz, 1H, *Naph*); 7.97 (d, J= 8.0 Hz, 1H, *Naph*); 8.02 (d, J= 8.8 Hz, 1H, *Naph*); 8.35 (s, 1H, *Naph*).

MS (EI) *m/z*: 239, 269, 396, 424.

HMRS (EI): *m/z* calcd. $[M]^+$= 423.9960, found $[M]^+$: 423.9959.

5.6.2.41. **Synthesis of (*S*)-(1,1'-binaphthalene)-6-(diacetoxy)iodo-2,2'-dioxepine.**



Scheme 263

Adapted from reported procedure[128].

To a mixture of $NaIO_4$ **428** (230 mg, 1.07 mmol), AcONa **429** (187 mg, 2.28 mmol), Ac_2O **430** (156 μL, 1.64 mmol) in AcOH (1.7 mL) at RT was added (*S*)-(1,1'-binaphthalene)-2,2'-dioxepine-6-iodo *S*-**343** (440 mg, 1.04 mmol) was refluxed for 2h. The reaction mixture was then poured into water. The resulting mixture was filtered, and the residue was washed with 10% aq AcOH (2 × 10 mL) and dried under a stream of air. It was successively washed with hexane to remove the remaining reagent and impurities; but the product was obtained in a complex mixture with the reagent on a ratio of 1:1.5 *S*-**341**: *S*-**343** (based on the integrations of *S*-**343**-^{1}H NMR peak δ 8.35 ppm- and *S*-**341**- ^{1}H NMR peak δ 8.77 ppm.

LRMS (ESI$^+$-TOF) *m/z* calcd. $[M+Na]^+$= 565.0119, found $[M+Na]^+$: 565.0110.

5.6.2.42. **General procedure for the antimicrobial activity assays**

Experience performed by Prof. Patrícia Rijo (Universidade Lusófona / iMed.UL).

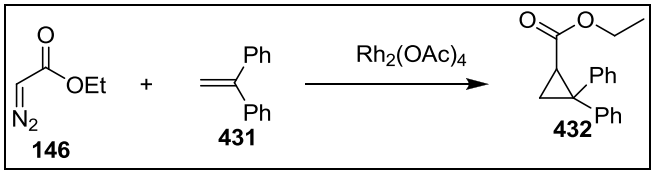
The well diffusion assay was used to screen the antimicrobial activity of the β-lactam compounds[2].

[2] CLSI- Clinical and Laboratory Standards Institute. (2011). Performance standards for antimicrobial susceptibility testing: Twenty First International Supplement M100-S21. Clinical and Laboratory Standards Institute, Wayne, PA.

Petri dishes containing 20 ml Mueller-Hinton culture medium were inoculated with 0.1 ml of a bacterial cell suspension matching a 0.5 McFarland standard solution. The suspension was uniformly spread using a sterile swab over the surface of the medium. Wells of approximately 5mm in diameter were made in the agar plates with a sterile glass Pasteur pipette and 50μL of each compound (1mg/ml), previously reconstituted by dissolving in DMSO, was added into the well. DMSO was used as a negative control, while vancomycin, norfloxacin and amphotericin B (1mg/ml) were used as positive controls for Gram-positive and Gram-negative bacteria and yeast, respectively. The plates were then incubated at 37ºC for 24 hours. The antimicrobial activity was assayed by measuring the diameter of the inhibition zone formed around the wells. Each assay was performed in triplicate.

5.6.3. Study of the Mechanism of Iodine (III)-mediated C-H Insertion/C-C Bond Formation

5.6.3.1. Synthesis of ethyl 2,2-diphenylcyclopropanecarboxylate



Scheme 264

Adapted from reported procedure and spectra data identical to those reported [143]

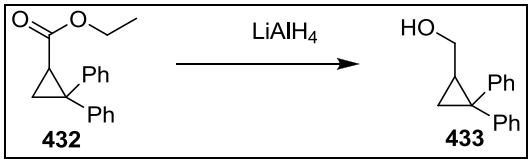
A dichloromethane ethyl diazoacetate **146** solution (415 μL, 3.95 mmol) was added during 4h, with a syringe pump, to a suspension of 1,1-diphenylethylene **431** (1.88 g, 10.4 mmol), $Rh_2(OAc)_4$ (3.4 mg. 7.7 μmol) in dichloromethane (9.4 mL) at room temperature. After 4.5h the solvent was evaporated and the residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). Ethyl 2,2-diphenylcyclopropanecarboxylate **432** was obtained as a white solid (1.12 g, quantitative).

R_f = 0.22 (silica, 5% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, J=7.2 Hz, 3H, OCH_2CH_3); 1.64-1.67 (m, 1H, COCHCH*H*); 2.24-2.27 (m, 1H, COCHC*H*H); 2.60-2.64 (m, 1H, COC*H*); 3.92-4.06 (m, 2H, CH_3CH_2); 7.20-7.36 (m, 10H, 2*Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.10 (OCH*2*C*H3*), 20.20 (COCH*C*H_2), 29.13 (CO*C*H), 39.89 (Ph*C*Ph), 60.51 (O*C*H_2CH_3), 126.58, 127.03, 127.65, 128.35, 128.52, 129.82, 140.33, 144.92 (2*Ph*), 170.67 (CH*C*OO).

5.6.3.2. Synthesis of (2,2-diphenylcyclopropyl)methanol



432 **433**

Scheme 265

Prepared following reported procedure and spectra data identical to those reported[143].

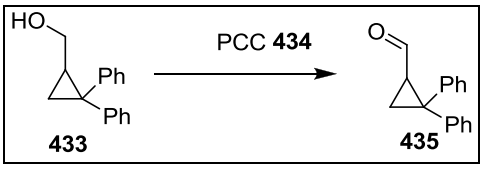
A solution of ethyl 2,2-diphenylcyclopropanecarboxylate **432** (1.12g, 4.2 mmol) in Et_2O (24 mL), was slowly added at 0 ºC to a suspension of $LiAlH_4$ (223 mg, 5.87 mmol) in Et_2O (18 mL) under stirring at 0 ºC. After the addition the reaction was warmed up to room temperature and after 1.25 h, H_2O was added and then aqueous NaOH (10 % m/m) solution. The mixture was extracted with Et_2O (3x), dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). (2,2-diphenylcyclopropyl)methanol **433** was obtained as a colorless viscous liquid (848 mg, 90 %).

R_f = 0.23 (silica, 20% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31-1.34 (m, 1H); 1.42 (t, J= 5.6 Hz); 1.65 (bs, 1H); 2.00-2.08 (m, 1H); 3.39-3.44 (m, 1H); 3.48-3.52 (m, 1H); 7.18-7.45 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.00, 27.77, 35.68, 63.83, 126.03, 126.74, 127.88, 128.34, 128.59, 130.17, 141.13, 146.33.

5.6.3.3. Synthesis of 2,2-diphenylcyclopropanecarbaldehyde



Scheme 266

Prepared following reported procedure and spectra data identical to those reported[143].

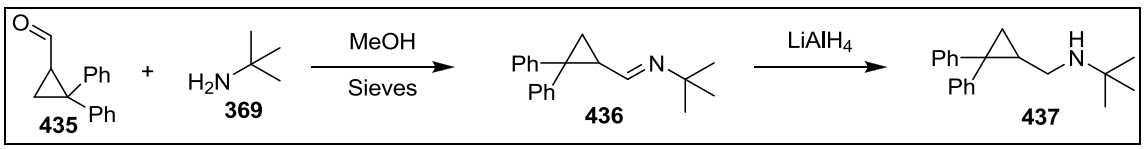
To a solution of (2,2-diphenylcyclopropyl)methanol **433** (497 mg, 2.22 mmol) in dichloromethane (11 mL), pyridinium chlorochromate **434** (0.868 g, 4.02 mmol) was added dissolved in dichloromethane (2 mL). The solution was stirred for 2.5h at room temperature. The reaction mixture was filtered over silica and repeatedly washed with Et_2O. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2,2-diphenylcyclopropanecarbaldehyde **435** was obtained as a colorless viscous liquid (436 mg, 88 %).

R_f = 0.73 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87-1.91 (m, 1H, COCHCH*H*); 2.26 (t, J= 5.6 Hz, 1H, COCHC*H*H); 2.54-2.58 (m, 1H, COC*H*); 7.17-7.42 (m, 10H, 2 *Ph*); 8.67 (d, J= 6.8 Hz, 1H, CO*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.24 (CH*C*H_2); 36.72 (CO*C*H); 40.91 (Ph*C*Ph); 126.90, 127.37, 127.48, 128.63, 128.90, 130.05, 139.41, 143.90 (2*Ph*); 200.45 (*C*O).

5.6.3.4. Synthesis of N-(*tert*-butyl)-N-((2,2-diphenylcyclopropyl)methyl)amine



Scheme 267

Adapted from general procedure[138]

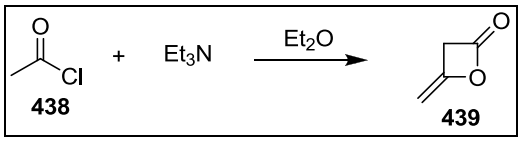
tert-Butylamine **369** (465 μL, 4.42 mmol) was added dropwise to a suspension of 2,2-diphenylcyclopropanecarbaldehyde **435** (654 mg, 2.94 mmol); 4Å sieves (2.6 g) in dry toluene (13 mL). The mixture was stirred at room temperature for 18 h. Then the sieves were filtrated over a celite pad, under Argon and repeatedly washed with dry Et_2O. The solvents were removed and the yellow solid was used on the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 9H); 1.67-1.71 (m, 1H); 1.81 (t, J= 5.6 Hz, 1H); 2.53-2.58 (m, 1H); 6.64 (d, J= 8.0 Hz, 1H); 7.09-7.40 (m, 10H).

The previously obtained imine **436** was dissolved in Et_2O (16.9 mL) and added dropwise to a suspension of $LiAlH_4$ (136 mg, 3.58 mmol) in Et_2O (13 mL). The mixture was stirred 1h at room temperature. H_2O was added and then aqueous NaOH (10 % m/m) solution. The mixture was extracted with Et_2O (3x), dried with anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified through silica gel chromatography 40% AcOEt in hexanes and then 5 % Et_3N in hexanes to collect the product. N-(*tert*-butyl)-N-((2,2-diphenylcyclopropyl)methyl)amine **437** was obtained as a colorless viscous liquid (769 mg, 94 % two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, NC(CH_3)$_3$); 1.22-1.26 (m, 1H, PhCCH*H*); 1.40 (t, J= 5.2 Hz, , PhCC*H*H); 1.92-1.99 (m, 1H, NCH_2CH); 2.30-2.42 (m, 2H, NCH_2); 7.25-7.38 (m, 10H, 2*Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): δ 18.86 (PhCHCH_2); 26.17 (CH_2CH); 28.77 (NC(CH_3)$_3$); 35.23 (Ph*C*); 43.71 (NCH_2); 50.01 (N*C*(CH_3)$_3$); 125.87, 126.40, 128.21, 128.22, 128.26, 130.02, 141.18, 146.75 (*Ph*).

5.6.3.5. **Synthesis of diketene**



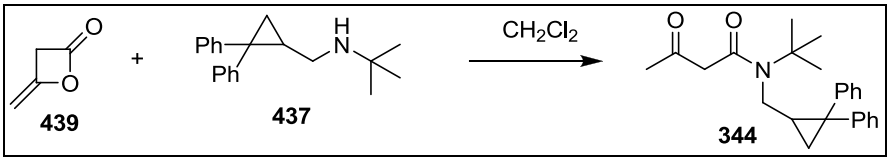
Scheme 268

Adapted from reported procedure[144].

To a solution of acetyl chloride **438** (5.6 mL, 78.4 mmol) in Et_2O (70 mL) was added Et_2N (11.2 mL, 80.3 mmol) while maintaining the reflux. The solution was further heated under reflux for 1h and was left stirring overnight. The mixture was filtered and washed with Et_2O, the solvents evaporated and the residue distilled at reduced pressure where diketene **439** (828 mg, 13 %) was collected at 50 Torr/ 65 ºC as an irritating liquid which solidifies in the freezer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (bs, 2H, $COCH_2$); 4.51-4.52 (m, 1H, C=CH*H*); 4.89 (bs, 1H, C=C*H*H).

5.6.3.6. **Synthesis of 2-(acetyl)-N-(*tert*-butyl)-N-((2,2-diphenylcyclopropyl)methyl)acetamide**



Scheme 269

Prepared following general procedure[6]

Diketene **439**[144] (118 mg, 1.40 mmol) was dissolved in dichloromethane (1 mL) and added to a solution of N-(*tert*-butyl)-N-((2,2-diphenylcyclopropyl)methyl)amide **437** (303 mg, 1.09 mmol) in dichloromethane (9 mL) at 0 ºC under stirring. After the addition the reaction was warmed up to room temperature and was stirred for 22 h. Then NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane

(3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(*tert*-butyl)-N-((2,2-diphenylcyclopropyl)methyl)acetamide **344** was obtained as a yellow viscous liquid (249 mg, 63%) and as a keto-enol equilibrium mixture (1:0.3).

R_f = 0.55 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36-1.40 (m, 1H, PhCCH*H* enol); 1.44-1.47 (m, 1H, PhCCH*H* keto); 1.49-1.53 (m; 9H, NC(C*H*$_3$)$_3$; 1H, PhCC*H*H keto); 1.59 (t, J= 5.2 Hz, 1H, PhCC*H*H enol); 1.75-1.813 (m, 1H, CH_2C*H* keto); 1.84-1.89 (m, 1H, CH_2C*H* enol); 1.92 (s, 3H, C*H*$_3$COH enol); 2.18 (s, 3H, C*H*$_3$CO keto); 2.56 (dd, J= 8.0 Hz, J= 16.4 Hz, 1H, NCH*H* keto); 2.66 (dd, J= 8.4 Hz, J= 16.4 Hz, 1H, NCH*H* enol); 3.35-3.44 (m, 2H, COC*H*$_2$CO); 3.53-3.58 (m, 1H, NC*H*H enol; 1H, NC*H*H keto); 4.93 (s, 1H, OC*H*CO enol); 7.18-7.38 (m, 10H, *2Ph*); 15.24 (s, 1H, CO*H* enol).

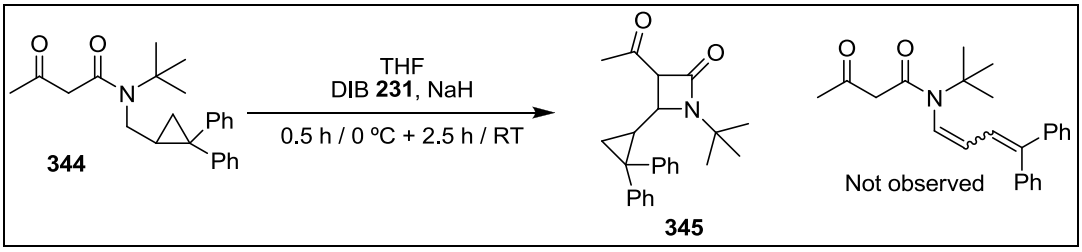
^{13}C NMR (100 MHz, $CDCl_3$): δ 20.75 (PhC*C*H_2 enol); 21.37 (PhC*C*H_2 keto); 22.24 (CH_3*C*O enol); 26.44 (NCH_2*C*H keto); 26.65 (NCH_2*C*H enol); 29.00 (NC(*C*H_3)$_3$ keto); 29.44, 30.08 (CH_3*C*O keto, NC(*C*H_3)$_3$ enol); 35.99 (Ph*C*CH keto); 36.24 (Ph*C*CH enol); 45.44 (N*C*H_2 enol); 46.85 (N*C*H_2 keto); 52.59 (CO*C*H_2CO); 57.01 (N*C*(CH_3)$_3$ enol); 57.53(N*C*(CH_3)$_3$ keto); 89.77 (HOCC*H* enol); 125.86, 126.18, 126.31, 126.41, 126.88, 127.03, 127.73, 127.80, 128.21, 128.24, 128.43, 128.49, 128.63., 128.78, 129.93, 130.04, 140.12, 140.42, 145.85, 146.16 (*2Ph*); 167.68 (N*C*O keto); 173.79 (*C*O enol); 174.33 (*C*O enol); 202.94 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2964, 1723, 1635, 1360, 1197, 754, 705

MS (EI) *m/z*: 206, 307

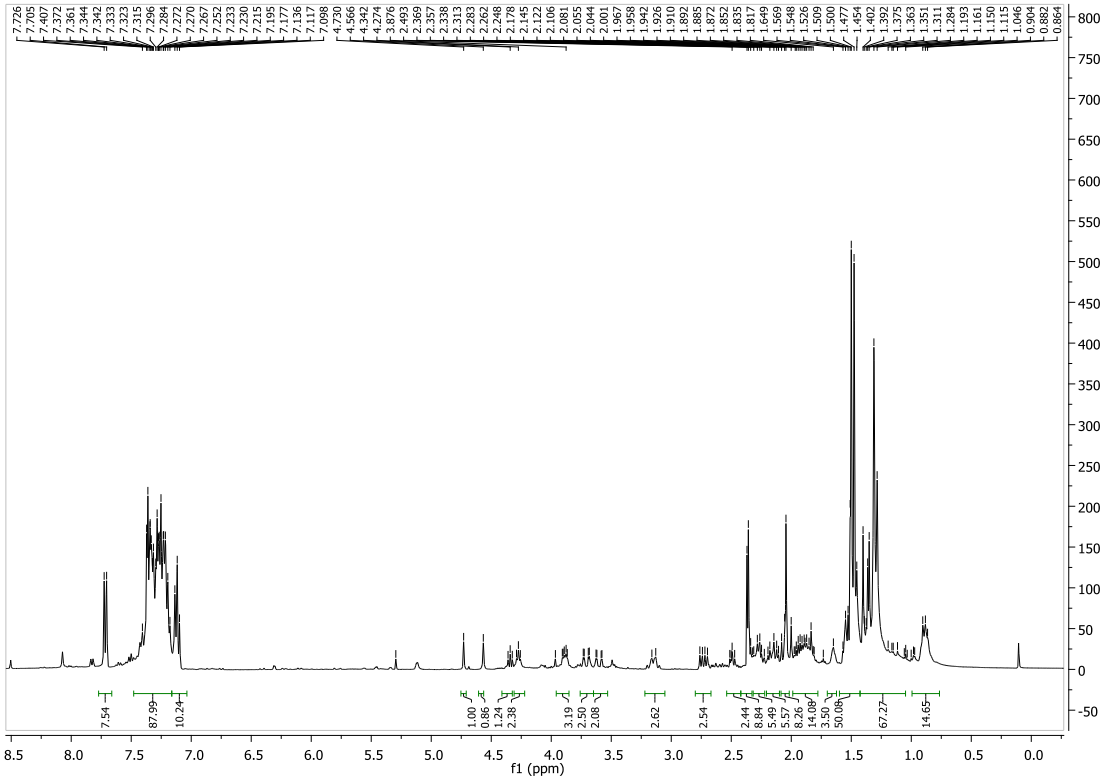
HMRS (ESI$^+$): *m/z* calcd. $[M+Na]^+$= 386.209047, found $[M+Na]^+$: 386.208734

5.6.3.7. **Reaction behavior of 2-(acetyl)-N-(*tert*-butyl)-N-((2,2-diphenylcyclopropyl)methyl)acetamide under iodine (III) mediated C-H insertion conditions**



Scheme 270

In a round bottom flask was placed (diacetoxyiodo)benzene **231**(88.7 mg, 0.275 mmol), followed by THF (2.0 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (12.3 mg, 0.308 mmol) was added followed by 2-(acetyl)-N-(*tert*-butyl)-N-((2,2-diphenylcyclopropyl)methyl)acetamide **344** (50.5 mg, 0.139 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (30 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. No ring-opening products were observed by crude ^1H NMR (Scheme 271). The residue was purified through neutral alumina flash chromatography (10% AcOEt in hexanes) but the product was still impure. Further purification by preparative neutral alumina TLC (10% AcOEt in hexanes) rendered 3-(acetyl)-1-(*tert*-butyl)-4-((2,2-diphenylcyclopropyl)methyl)-β-lactam **345** as a white solid (2.2 mg, 4%).



Scheme 271: ^{1}H NMR, $CDCl_3$ spectra of reaction crude mixture; the olefinic region (5.2 – 6.8 ppm) is clear.

R_f = 0.24 (silica, 20% AcOEt in hexanes).

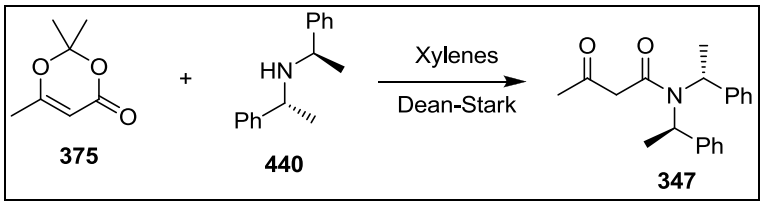
^{1}H NMR (400 MHz, $CDCl_3$): δ 1. 40 (s; 9H, NC(CH_3)$_3$); 1.43-1.47 (m, 1H, PhCCH*H*); 1.73 (t, J= 5.6 Hz, 1H, , PhCC*H*H); 1.83-1.89 (m, 1H, PhCC*H*); 2.00 (s, 3H, CH_3CO); 3.12 (dd, J= 1.6 Hz, J= 9.6 Hz, 1H, NC*H*); 3.95 (d, J= 1.2 Hz, 1H, COC*H*CO); 7.16-7.36 (m, 10H, *2Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.35 (PhC*C*H$_2$); 28.31 (PhC*C*H); 28.60 (NC(*C*H$_3$)$_3$); 29.23 (*C*H$_3$CO); 39.95 (Ph*C*CH); 54.31 (N*C*(CH$_3$)$_3$); 55.28 (N*C*H); 68.08 (CO*C*HCO); 126.54, 127.01, 128.24, 128.53, 128.64, 129.09, 139.40, 145.30 (*Ph*); 161.71 (N*C*O); 198.64 (CH$_3$*C*O).

MS (ESI^{+}-TOF) *m/z*: 129, 167, 263, 280

HMRS (ESI^{+}-TOF): *m/z* calcd. [M+Na]$^{+}$= 384.1934, found [M+Na]$^{+}$: 384.1934.

5.6.3.8. Synthesis of 2-(acetyl)-bis((*R*)-1-phenylethyl)acetamide



Scheme 272

Prepared following general procedure[132]

In a round bottom flask, (+)-bis((*R*)-1-phenylethyl)amine **440** (400 mg, 1.78 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (228 mg, 1.6 mmol) in xylenes (3 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-bis((*R*)-1-phenylethyl)acetamide **347** was obtained as a yellow viscous liquid (438 mg, 80 %) and as a keto-enol equilibrium mixture (1:0.37).

The other enantiomer, 2-(acetyl)-bis((*S*)-1-phenylethyl)acetamide **348** (70 %), was synthesized from (-)-bis((*S*)-1-phenylethyl)amine and provided the same spectral data.

R_f = 0.31 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74-1.78 (m, 6H, NCHC*H*$_3$ keto, NCHC*H*$_3$ enol, C*H*$_3$COH enol); 2.10 (s, 3H, C*H*$_3$CO keto); 3.31 (s, 2H, COC*H*$_2$CO keto); 4.47 (s, 2H, COC*H*CO enol); 4.89-4.90 (m, 2H, NC*H*); 5.68 (bs, 2H, NC*H*); 6.99-7.26 (m, 10H, *2Ph*); 14.86 (s, 1H, CH_3CO*H* enol).

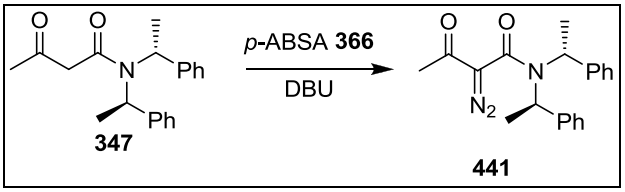
^{13}C NMR (100 MHz, $CDCl_3$): δ 17.79, 19.63, 22.06 (NCH*C*H$_3$ keto, NCH*C*H$_3$ enol, *C*H$_3$CO enol); 30.20 (*C*H$_3$CO keto); 51.69 (N*C*H); 51.84(CO*C*H$_2$CO); 52.76, 52.91 (N*C*H); 90.59 (CO*C*HCO enol); 126.68, 126.75, 127.46, 127.55, 128.12, 128.24, 128.41, 128.57, 140.55, 140.84 (*2Ph*); 167.15 (N*C*O keto); 172.03, 173.99 (CO enol); 202.56 (CH_3*C*O).

IR (neat, cm^{-1}): 2979, 1718, 1632, 1437, 1274, 776, 698

MS (EI) *m/z*: 43, 205, 204, 266

HMRS (ESI$^+$): *m/z* calcd. $[M+Na]^+$= 332.162097, found $[M+Na]^+$: 332.161891

5.6.3.9. **Synthesis of 2-(acetyl)-2-diazo-bis((*R*)-1-phenylethyl)acetamide**



Scheme 273

Adapted from reported procedure[131]

DBU (80 μL, 0.535 mmol) was added dropwise to a mixture of 2-(acetyl)-bis((*R*)-1-phenylethyl)acetamide **347** (149 mg, 0.482 mmol), *p*-ABSA **366** (128 mg, 0.533 mmol) in acetonitrile (2 mL) at 0ºC. The solution was stirred at that temperature for 0.5h and the solvent was evaporated. The residue was purified through silica gel chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-2-diazo-bis((*R*)-1-phenylethyl)acetamide **441** was obtained as a yellow viscous liquid (158 mg, 98%).

The other enantiomer, 2-(acetyl)-2-diazo-bis((*S*)-1-phenylethyl)acetamide (153 mg, 94 %), was synthesized from 2-(acetyl)-bis((*S*)-1-phenylethyl)acetamide **348** and provided the same spectral data.

R_f = 0.25 (silica, 20% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (d, J= 7.2 Hz, 6H, NCHC*H*$_3$); 2.30 (s, 3H, C*H*$_3$CO); 4.95 (q, J= 6.8 Hz, 2H, NC*H*); 7.15-7.28 (m, 10H, *2Ph*).

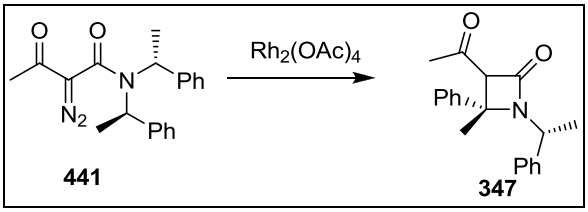
^{13}C NMR (100 MHz, $CDCl_3$): δ 18.62 (NCH*C*H$_3$); 26.94 (*C*H$_3$CO); 55.94 (N*C*H); 127.54, 127.72, 128.25, 140.05 (*Ph*); 160.00 (N*C*O).

IR (neat, cm^{-1}): 2979, 2101, 1653, 1425, 1308, 679

MS (ESI^+-TOF) *m/z*: 183, 246, 287, 302

HMRS (ESI^+-TOF): *m/z* calcd. $[M+Na]^+$= 358.1520, found $[M+Na]^+$: 358.1526.

5.6.3.10. **Reaction of 2-(acetyl)-2-diazo-bis((*R*)-1-phenylethyl)acetamide with $Rh_2(OAc)_4$**



Scheme 274

Prepared for standard creation by Rh(II)- catalyzed C-H insertion of diazo substrate.

To a solution of 2-(acetyl)-2-diazo-bis((*R*)-1-phenylethyl)acetamide **441** (50.0 mg, 0.149 mmol) in dichloromethane (3 mL) was added $Rh_2(OAc)_4$ **1** (1.5 mg, 3.4 μmol). The solution was stirred under reflux for 3h. The solvent was evaporated and the residue purified through neutral alumina flash chromatography (15% AcOEt in hexanes, gradient) where 3-(acetyl)-(*S*)-4-methylphenyl-N-[(*R*)-1-phenylethyl]-β-lactam **347** was isolated as a colourless liquid (30.5 mg, 67%) and a mixture of *cis*/*trans* diastereomers (2A:1B).

The other enantiomer, 3-(acetyl)-(*R*)-4-methylphenyl-N-[(*S*)-1-phenylethyl]-β-lactam **349** (38 %), was synthesized from 2-(acetyl)-2-diazo-bis((*S*)-1-phenylethyl)acetamide and provided the same spectral data.

R_f = 0.31 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (d, J= 7.2 Hz, 3H, A PhCHC*H*$_3$); 1.72-1.74 (m, 6H, B PhCHC*H*$_3$ and C*H*$_3$CO); 1.78 (s, 3H, A PhCC*H*$_3$); 1.94 (s, 3H, PhCC*H*$_3$); 2.32 (s, 3H, A C*H*$_3$CO); 3.96 (s, 1H, A COC*H*CO); 3.99 (s, 1H, B COC*H*CO); 4.40-4.48 (m, 1H, A and B PhC*H*CH$_3$); 7.13-7.49 (m, 10H, A and B *2Ph*).

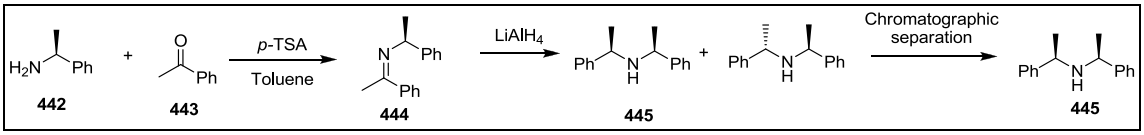
^{13}C NMR (100 MHz, $CDCl_3$): δ 20.66 (A PhC*C*H$_3$); 21.10 (A PhCH*C*H$_3$); 21.54 (B PhCH*C*H$_3$); 25.22 (B PhC*C*H$_3$); 30.02 (B *C*H$_3$CO); 31.06 (A *C*H$_3$CO); 54.28 (A Ph*C*HCH$_3$); 54.92 (B Ph*C*HCH$_3$); 63.93 (A N*C*Ph); 64.99 (B N*C*Ph); 72.41 (A CO*C*HCO); 73.52 (B CO*C*HCO); 125.52, 126.57, 127.36, 127.39, 127.59, 127.63, 127.87, 128.08, 128.42, 128.57, 128.60, 128.74, 138.52, 141.69, 141.92, 142.03 (*2Ph*); 164.07 (N*C*O); 201.07 (A CH$_3$*C*O); 201.12 (B CH$_3$*C*O).

IR (neat, cm^{-1}): 2978, 1749, 1709, 1348, 759, 700

MS (EI) *m/z*: 43, 105, 202, 264.

HMRS (ESI^+): *m/z* calcd. $[M+Na]^+$= 330.146450, found $[M+Na]^+$: 330.146366

5.6.3.11. Synthesis of bis((*R*,*S*)-1-phenylethyl)amine



Scheme 275

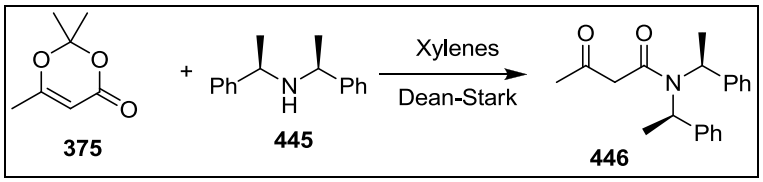
Adapted from reported procedure[145]

(*S*)-(−)-α-Methylbenzylamine **442** (1.90 g, 15.7 mmol), was added to a suspension of 4Å sieves (19 g), acetophenone **443** (2.73 g, 22.7 mmol), *p*-toluenesulfonic acid monohydrate (316 mg, 1.66 mmol) in toluene (30 mL). The suspension was stirred at reflux during 5 days, then it was cooled down and filtered through a celite pad and repeatedly washed with dichloromethane. After dichloromethane removal at reduced pressure it was washed with a cold aqueous diluted solution of $NaHCO_3$ (4 mL), cold brine and dried with anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was dissolved in THF (20 mL), added to a suspension of $LiAlH_4$ (812 mg, 21.4 mmol) in THF (120 mL) and refluxed for 20 h. Then water was added (2 mL) and the precipitate washed with plenty Et_2O. The solvents were removed under reduced pressure and after successive silica gel automatic chromatography (AcOEt/hexanes) the enriched bis((*R*,*S*)-1-phenylethyl)amine **445** was obtained as a colorless liquid (63 mg, 2%), with traces of bis((*S*,*S*)-1-phenylethyl)amine due to impossible complete isolation.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, J= 6.4 Hz, 6H, NCHC*H*$_3$); 3.86 (q, J= 6.8 Hz, 2H, NC*H*); 7.29-7.41 (m, 10H, *2Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.13 (NCH*C*H$_3$); 54.95 (N*C*H); 126.68, 126.95, 128.50, 145.77 (*Ph*).

5.6.3.12. **Synthesis of 2-(acetyl)-bis((*R*,*S*)-1-phenylethyl)acetamide**



Scheme 276

Prepared following general procedure[132]

In a round bottom flask, bis((*R*,*S*)-1-phenylethyl)amine **445** (54 mg, 0.240 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (36 mg, 0.254 mmol) in xylenes (1 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-bis((*R*,*S*)-1-phenylethyl)acetamide **446** was obtained as a yellow viscous liquid (59 mg, 80 %) and as a keto-enol equilibrium mixture (1:0.34).

R_f = 0.21 (silica, 10% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J= 6.4 Hz, 3H, NCHC*H*$_3$); 1.59 (d, J= 6.8 Hz, 3H, NCHC*H*$_3$); 1.81 (s, 3H, C*H*$_3$CO enol); 2.17 (s, 3H, C*H*$_3$CO keto); 3.32-3.37 (m, 2H, COC*H*$_2$CO); 4.78-4.81 (m, 1H, NC*H*); 5.66 (bs, 1H, NC*H*); 7.26-7.42 (m, 10H, *2Ph*); 14.89 (s, 1H, CH_3CO*H* enol).

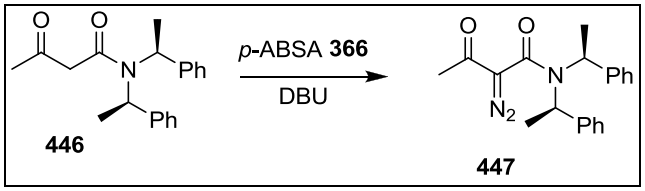
^{13}C NMR (100 MHz, $CDCl_3$): δ 17.21, 19.18 (NCH*C*H$_3$); 22.08 (*C*H$_3$CO enol); 30.07 (*C*H$_3$CO keto); 52.00 (CO*C*H$_2$CO); 52.65, 53.47 (N*C*H); 90.93 (CO*C*HCO enol); 126.40, 126.61, 127.16, 127.31, 127.53, 128.39, 128.47, 128.88, 141.28, 141.52 (*2Ph*); 167.41 (N*C*O keto); 172.23, 174.04 (*C*O enol); 202.54 (CH_3*C*O keto).

IR (neat, cm^{-1}): 2980, 1714, 1632, 1445, 1272, 777, 699

MS (EI) *m/z*: 105, 120, 204

HMRS (ESI$^+$): *m/z* calcd. $[M+Na]^+$= 332.162096, found $[M+Na]^+$: 332.161989

5.6.3.13. **Synthesis of 2-(acetyl)-2-diazo-bis((*R*,*S*)-1-phenylethyl)acetamide**



Scheme 277

Adapted from reported procedure[131]

DBU (37 μL, 0.247 mmol) was added dropwise to a mixture of 2-(acetyl)-bis((*R*,*S*)-1-phenylethyl)acetamide **446** (69 mg, 0.223 mmol), *p*-ABSA **366** (59 mg, 0.246 mmol) in acetonitrile (1 mL) at 0ºC. The solution was stirred at that temperature for 0.5h and the solvent was evaporated. The residue was purified through silica gel chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-2-diazo-bis((*R*,*S*)-1-phenylethyl)acetamide **447** was obtained as a yellow viscous liquid (50 mg, 69%).

R_f = 0.47 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, J= 6.8 Hz, 6H, NCHC*H*$_3$); 2.38 (s, 3H, C*H*$_3$CO); 4.85 (q, J= 6.8 Hz, 2H, NC*H*); 7.24-7.42 (m, 10H, *2Ph*)

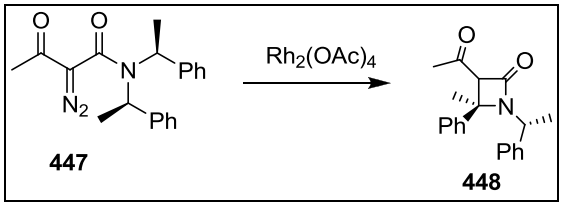
^{13}C NMR (100 MHz, $CDCl_3$): δ 17.40 (NCH*C*H$_3$); 27.14 (*C*H$_3$CO); 55.99 (N*C*H); 127.01, 127.69, 128.56, 140.66 (*Ph*); 160.04 (N*C*O).

IR (neat, cm^{-1}): 2980, 2104, 1653, 1425, 1309, 763, 699, 604

MS (EI) *m/z*: 226, 246, 287

HMRS (ESI$^+$-TOF): *m/z* calcd. $[M+Na-N_2]^+$= 330.1467, found $[M+Na-N_2]^+$: 330.1465

5.6.3.14. **Reaction of 2-(acetyl)-2-diazo-bis((*R,S*)-1-phenylethyl)acetamide with $Rh_2(OAc)_4$**



Scheme 278

Prepared for standard creation by Rh(II)- catalyzed C-H insertion of diazo substrate.

To a solution of 2-(acetyl)-2-diazo-bis((*R,S*)-1-phenylethyl)acetamide **447** (50.0 mg, 0.149 mmol) in dichloromethane (3 mL) was added $Rh_2(OAc)_4$ (1.6 mg, 3.6 μmol). The solution was stirred under reflux for 2h. The solvent was evaporated and the residue purified through neutral alumina flash chromatography (15% AcOEt in hexanes, gradient) where 3-(acetyl)-(*R*)-4-methylphenyl-N-[(*R*)-1-phenylethyl]-β-lactam **448** was isolated as a white solid (28.2 mg, 61%) and a mixture of cis/trans diastereomers (2A:1B).

Traces of the chiral compound were found (RP-HPLC, Scheme 158 right) due to the impossible complete isolation of bis((*R,S*)-1-phenylethyl)amine. Dirhodium (II)-catalyzed reactions with diazos on C-H insertion / C-C bond formation have full retention of configuration[28].

R_f = 0.29 (silica, 25% AcOEt in hexanes).

m. p.= 75-78 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H, A PhCC*H*$_3$); 1.59 (s, 3H, B PhCC*H*$_3$ or C*H*$_3$CO); 1.81 (s, 3H, B C*H*$_3$CO or PhCC*H*$_3$); 1.92 (d, J= 7.2 Hz, A PhCHC*H*$_3$); 1.99 (d, J= 7.2 Hz, B PhCHC*H*$_3$); 2.30 (s, 3H, A PhCC*H*$_3$); 3.95 (s, 3H, A and B COC*H*CO); 4.06 (q, J= 7.2 Hz, 1H, A PhC*H*CH$_3$); 4.14 (q, J= 7.2 Hz, 1H, B PhC*H*CH$_3$); 7.25-7.48 (m, 10H, A and B *Ph*)

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.65 (A Ph*C*CH$_3$); 22.03 (B PhCH*C*H$_3$); 22.07 (A PhCH*C*H$_3$); 25.33, 30.29 (B *C*H$_3$CO and PhC*C*H$_3$); 31.13 (A *C*H$_3$CO); 55.44 (A and B Ph*C*HCH$_3$); 63.21 (A Ph*C*CH$_3$); 64.36 (A Ph*C*CH$_3$); 72.65 (A CO*C*HCO); 73.44 (B

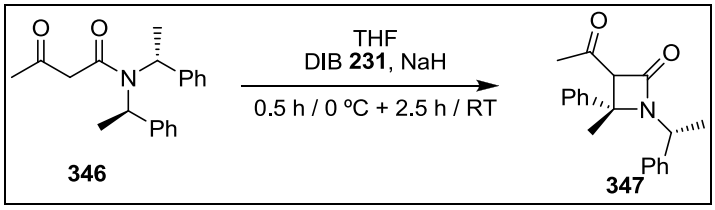
CO*C*HCO); 125.27, 126.44, 126.57, 126.76, 127.56, 127.64, 128.21, 128.40, 128.77, 128.86, 129.13, 128.11, 141.70, 143.41, 143.50 (A and B *Ph*); 163.82 (B N*C*O); 164.02 (A N*C*O); 200.87 (B CH_3*C*O); 201.14 (A CH_3*C*O).

IR (neat, cm^{-1}): 2978, 1747, 1709, 1349, 759, 701

MS (EI) *m/z*: 107, 149, 191

HMRS (ESI^+-TOF): *m/z* calcd. $[M+Na]^+$= 271.1529, found $[M+Na]^+$: 271.1527

5.6.3.15. **Reaction behavior of 2-(acetyl)-bis((*R*)-1-phenylethyl)acetamide under iodine (III) mediated C-H insertion conditions**



Scheme 279

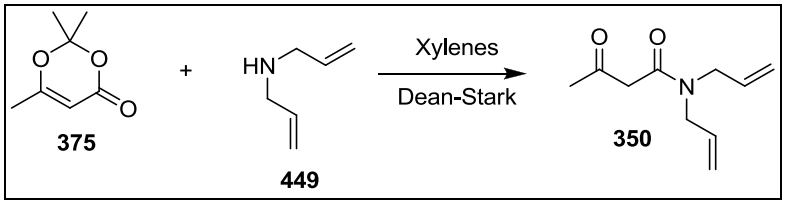
In a round bottom flask was placed (diacetoxyiodo)benzene **231** (80 mg, 0.248 mmol), followed by THF (2.3 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (15 mg, 0.375 mmol) was added followed by 2-(acetyl)-bis((*R*)-1-phenylethyl)acetamide **346** (50 mg, 0.162 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (15% AcOEt in hexanes) where 3-(acetyl)-(*S*)-4-methylphenyl-N-[(*R*)-1-phenylethyl]-β-lactam **347** was isolated as a yellow liquid (19 mg, 39%) and a mixture of cis/trans diastereomers (2A:1B).

The NMR (Scheme 156) and MS/HRMS characterization matched the one obtained with the respective Rh catalyzed diazo substrate decomposition, the *cis*/*trans* ratio is

equal and also the RP-HPLC (Scheme 158, left) of both standard and sample has the same retention time.

A similar procedure was used for 2-(acetyl)-bis((*S*)-1-phenylethyl)acetamide **348** providing similar results.

5.6.3.16. Synthesis of 2-(acetyl)-(diallylamine)acetamide



Scheme 280

Prepared following general procedure[132] and obtained as previously described[146]

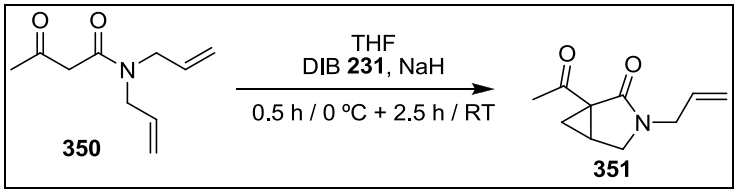
In a round bottom flask, diallylamine **449** (170 mg, 1.75 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (202 mg, 1.42 mmol) in xylenes (1.5 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-(diallylamine)acetamide **350** was obtained as a brown viscous liquid (244 mg, 96%) and as a keto-enol equilibrium mixture (1:0.3).

R_f = 0.28 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 3H, C*H*$_3$CO enol); 2.24 (s, 3H, C*H*$_3$CO keto); 3.50 (s, 2H, COC*H*$_2$CO); 3.81-3.82 (m, 2H, NC*H*$_2$); 3.96-3.97 (m, 2H, NC*H*$_2$); 5.03 (s, 1H, NCOC*H* enol); 5.10-5.21 (m, 4H, NCH_2CHCH_2); 5.70-5.82 (m, 2H, NCH_2CHCH_2); 14.62 (s, 1H, CH_3COH enol).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.97 (*C*H_3CO enol); 30.32 (*C*H_3CO keto); 47.91 (N*C*H_2); 49.73 (CO*C*H_2CO, N*C*H_2); 87.08 (NCO*C*H enol); 116.92, 117.48 (NCH_2CHCH_2); 132.49, 132.50 (NCH_2CHCH_2); 166.72 (N*C*O keto); 171.94 (*C*O enol); 175.05 (*C*O enol); 205.52 (CH_3CO keto).

5.6.3.17. **Reaction behavior of 2-(acetyl)-(diallylamine)acetamide under iodine (III) mediated C-H insertion conditions**



Scheme 281

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (130.6 mg, 0.406 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.8 mg, 0.620 mmol) was added followed by 2-(acetyl)-(diallylamine)acetamide **350** (48.5 mg, 0.267 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (40% AcOEt in hexanes) where the product **351** was isolated as a brown viscous liquid (18.5 mg, 39%).

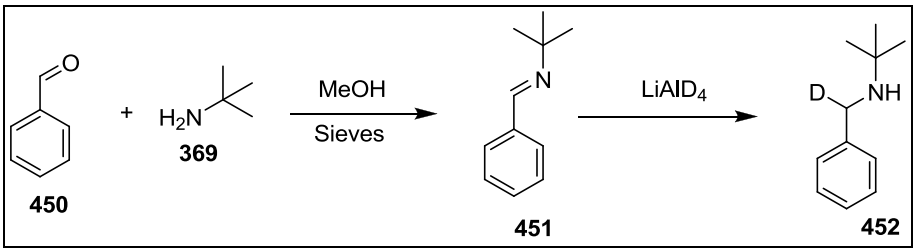
Spectral data obtained as previously reported[146]

R_f = 0.24 (silica, 40% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10-1.12 (m, 1H, COCCH*H*); 1.94 (dd, J= 3.6 Hz, J= 8.0 Hz, COCC*H*H); 2.39-2.44 (m, 1H, NCH_2C*H*CCO); 2.57 (s, 3H, C*H*$_3$CO); 3.22 (d, J= 10.8 Hz, 1H, NCH*H*CHCCO); 3.49 (dd, J= 5.6 Hz, J= 10.4 Hz, 1H, NC*H*HCHCCO); 3.76-3.89 (m, 2H, NC*H*$_2$ non cyclic); 5.14-5.21 (m, 2H, C*H*$_2$CHCH$_2$N non cyclic); 5.63-5.73 (m, 1H, CH_2C*H*CH_2N non cyclic).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.48 (COC*C*H$_2$); 25.07 (COC*C*H); 29.65 (*C*H$_3$CO); 39.15 (CO*C*CO); 45.10 (CH_2CHCH_2N non cyclic); 46.75 (COCCH*C*H$_2$N); 118.40 (*C*H$_2$CHCH$_2$N non cyclic); 132.14 (CH_2*C*HCH$_2$N non cyclic); 170.84 (N*C*O); 203.38 (CH$_3$*C*O).

5.6.3.18. Synthesis of N-(*tert*-butyl)-N-((^{2}H)methylphenyl)amine



Scheme 282

Benzaldehyde **450** (623 μL, 6.15 mmol) was added to a solution of activated 4Å granular sieves (3.2 g), *tert*-butylamine **369** (718 μL, 6.83mmol) in MeOH (31mL). The solution was stirred overnight at room temperature. On the next day the sieves were carefully filtrated under celite and Argon. The volatile compounds were evaporated affording N-Benzyl-*tert*-butylimine **451**.

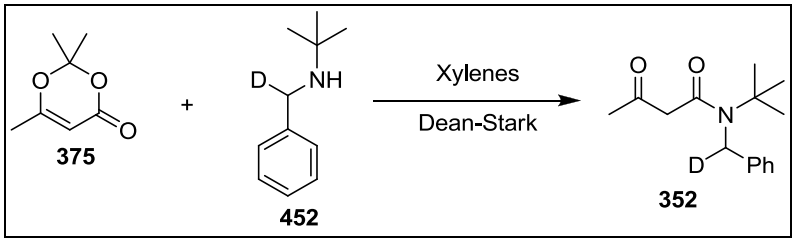
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H, NC(CH_3)$_3$); 7.42-7.45 (m, 3H, *Ph*); 7.76-7.80 (m, 2H, *Ph*); 8.31 (s, 1H, NC*H*).

$LiAlD_4$ (115 mg, 2.73 mmol) was added to a solution of N-Benzyl-*tert*-butylimine **451** (302 mg, 1.88 mmol) in THF (3 mL) and the suspension was stirred under reflux for 40 h, when more THF (8 mL) was added to prevent reaction dryness. More $LiAlD_4$ (41 mg, 0.98 mmol) was added and the reaction was again stirred under reflux overnight. H_2O was added and then a solution of aqueous NaOH (10 % m/m). The mixture was extracted with Et_2O (3x), dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). N-(*tert*-butyl)-N-((^{2}H)methylphenyl)amine **452** was obtained as a colorless liquid (98 mg, 32 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H, NC(CH_3)$_3$); 3.74 (s, 1H, PhC*H*D), 7.24-7.38 (m, 5H, *Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.18 (NC(*C*H_3)$_3$); 46.95 (t, $J_{C\text{-}D}$= 20.3 Hz, Ph*C*HD); 50.67 N*C*(CH_3); 126.72, 128.24, 128.40, 141.45 (*Ph*).

5.6.3.19. Synthesis of 2-(acetyl)-N-(*tert*-butyl)-N-((^{2}H)methylphenyl)acetamide



Scheme 283

In a round bottom flask, N-(*tert*-butyl)-N-((^{2}H)methylphenyl)amine **452** (78 mg, 0.476 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (92 mg, 0.648 mmol) in xylenes (1 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(*tert*-butyl)-N-((^{2}H)methylphenyl)acetamide **352** was obtained as a colorless liquid (87 mg, 74 %) and as a keto-enol equilibrium mixture (1:0.28).

R_f = 0.20 (silica, 10% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, NC(CH_3)$_3$); 1.83 (s, 3H, CH_3CO enol); 2.23 (s, 3H, CH_3CO keto); 3.45 (s, 2H, $COCH_2CO$); 4.55 (s, 1H, NC*H*D); 4.95 (s, 1H, NCOC*H* enol); 7.20-7.39(m, 5H, *Ph*); 15.08 (s, 1H, CH_3COH enol).

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.10 (CH_3CO enol); 28.57 (NC(CH_3)$_3$ keto); 28.92 (NC(CH_3)$_3$ enol); 30.40 (CH_3CO keto); 48.35-49.07 (m, NCHD enol, NCHD ketone); 89.81 (NCOCH enol); 125.43, 125.78, 126.94, 127.27, 128.72, 128.94, 138.62, 139.19 (*Ph*); 168.42 (NCO keto); 174.85 (CO enol); 174.90 (CO enol); 203.20 (CH_3CO keto).

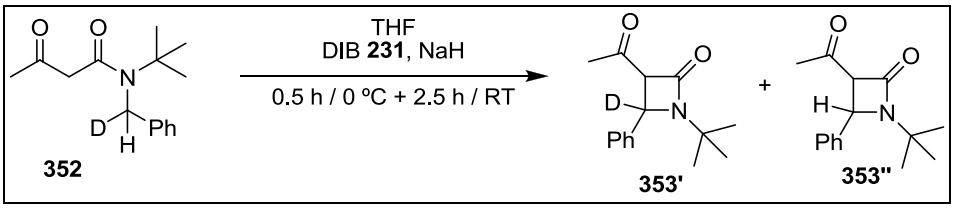
IR (neat, cm^{-1}): 2976, 1648, 1361, 1194, 729, 702

MS (EI) *m/z*: 107, 149, 191

HMRS (ESI$^+$-TOF): *m/z* calcd. $[M+Na]^+$= 271.1529, found $[M+Na]^+$: 271.1527

97% of deuterium incorporation by HRMS (ESI$^+$-TOF).

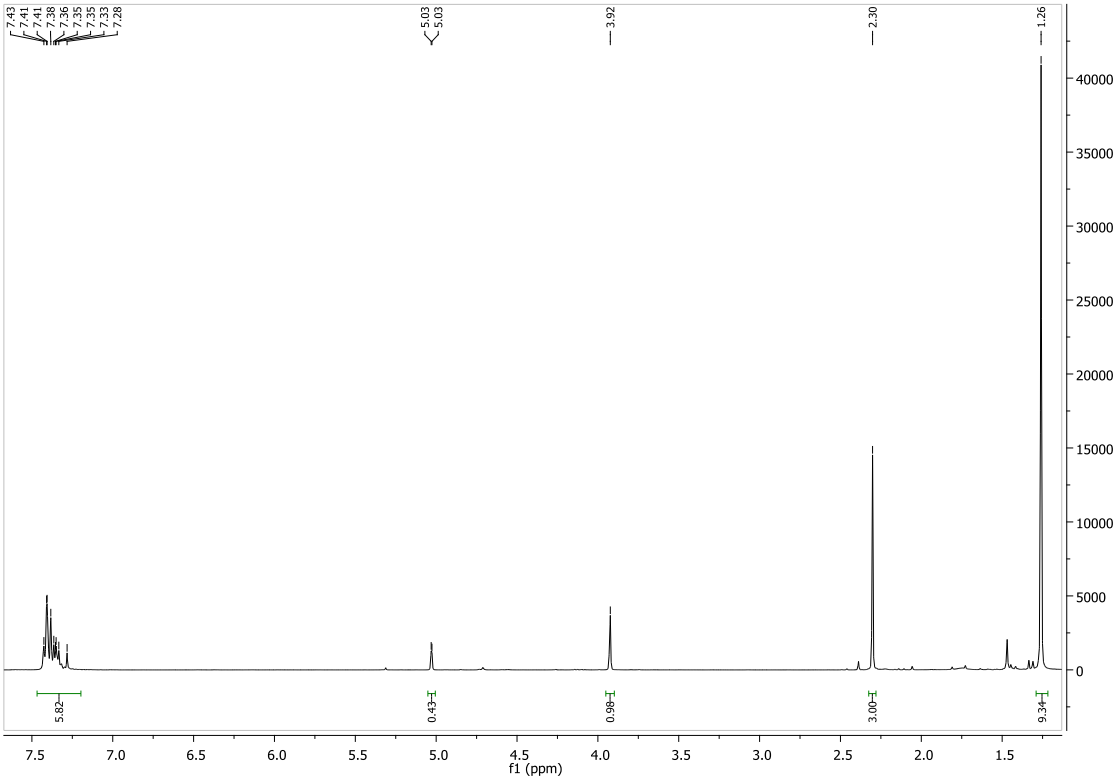
5.6.3.20. **Reaction behavior of 2-(acetyl)-N-(*tert*-butyl)-N-(([^{2}H)methylphenyl)acetamide under iodine (III) mediated C-H insertion conditions**



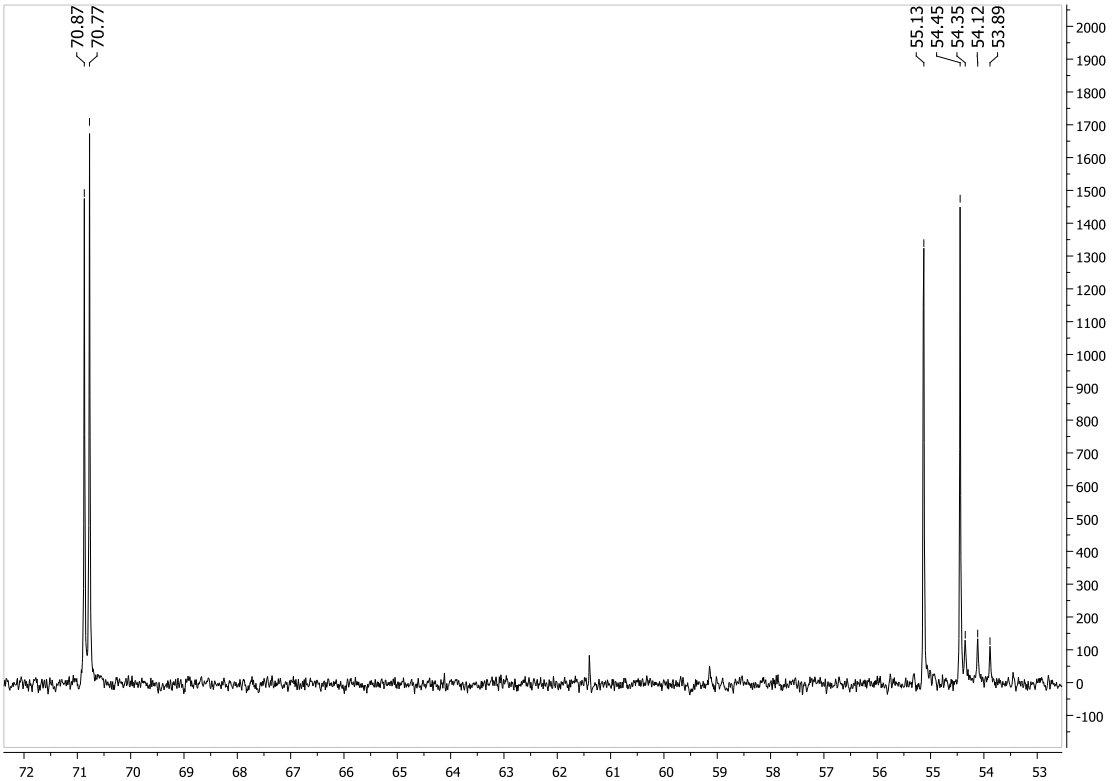
Scheme 284

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (131.1 mg, 0.407 mmol), followed by THF (2.9 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (20.1 mg, 0.503 mmol) was added followed by 2-(acetyl)-N-(*tert*-butyl)-N-(([^{2}H)methylphenyl)acetamide **352** (49.6 mg, 0.200 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (25 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (5% AcOEt in hexanes, gradient) providing a mixture of *trans*-3-(acetyl)-1-(*tert*-butyl)-4-phenyl-β-lactam **353'' ** and *trans*-3-(acetyl)-1-(*tert*-butyl)-4-([^{2}H)-4-phenyl-β-lactam **353'** as a brown solid (18.7 mg, 38%).

Since the carbonyl's α position is labile fully deuteride replacement by proton was found on the migrating deuteride. The kinetic isotopic effect (KIE) value was calculated based on the ^{1}H NMR integration of the the non-labile amide's α proton/deuterium and confirmed by HRMS.



Scheme 285: ^{1}H NMR, $CDCl_3$ spectra of compounds **353'** and **353''** mixture.



Scheme 286: ^{13}C NMR, $CDCl_3$ spectra expansion of compounds **353'** and **353''** mixture.

1-0.43=0.57

KIE = 1.3

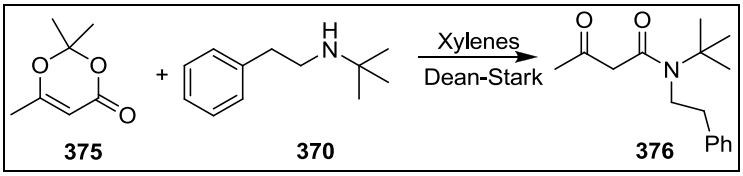
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H, NC(CH_3)$_3$), 2.30 (s, 3H, CH_3CO), 3.93 (bs, 1H, PhC*H*N); 5.03 (d, J= 2.0Hz, 0.43 H, NC*H*); 7.28-7.43 (m, 5H, *Ph*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.12 (NC(CH_3)$_3$); 30.09 (CH_3CO); 54.12 (t, J= 23.1 Hz, N*C*D); 54.45(NCH non deuterated); 55.13 (N*C*(CH_3)$_3$); 70.77, 70.87 (CO*C*HCO deuterated and non deuterated); 126.64, 128.56, 128.94, 139.25, 139.33 (*Ph*); 163.04 (N*C*O); 199.82 (CH_3*C*O).

MS (EI) *m/z*: 132, 146, 188

HMRS for $C_{15}H_{18}DNNaO_2$ (ESI$^+$-TOF): *m/z* calcd. $[M+Na]^+$= 269.1377, found $[M+Na]^+$: 269.1371.

5.6.3.21. Synthesis of N-(*tert*-butyl)-2-(acetyl)-N-(phenylethyl)acetamide



Scheme 287

Prepared following general procedure[132]

In a round bottom flask, N-(*tert*-butyl)-N-(phenylethyl)amine **370** (430 mg, 2.43 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (359 mg, 1.46 mmol) in xylenes (2.5 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120 ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). N-(*tert*-butyl)-2-(acetyl)-N-(phenylethyl)acetamide **376** was obtained as a brown viscous liquid (365 mg, 57%) and as a keto-enol equilibrium mixture (1:0.25).

R_f = 0.35 (silica, 20% AcOEt in hexanes).

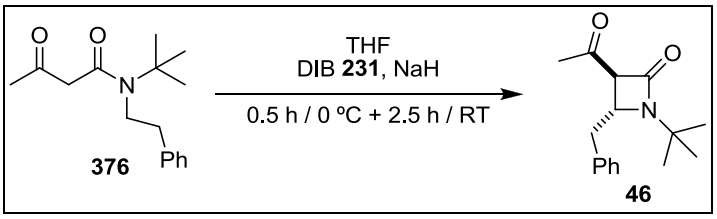
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 9H, NC(CH_3)$_3$); 1.98 (s, 3H, CH_3CO enol); 2.25 (s, 3H, CH_3CO keto); 2.83-2.90 (m, 2H, NCH_2CH_2); 3.45-3.52 (m, 4H, $COCH_2CO$, NCH_2CH_2 overlapped); 5.18 (s, 1H, NCOC*H* enol); 7.19-7.36 (*Ph*); 15.32 (s, 1H, CH_3COH enol).

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.41 (CH_3CO enol); 28.96 (NC(CH_3)$_3$ keto); 29.40 (NC(CH_3)$_3$ enol); 30.23 (CH_3CO keto); 37.71 (NCH_2CH_2 enol); 38.25 (NCH_2CH_2 keto); 46.57 (NCH_2CH_2 enol); 47.64 (NCH_2CH_2 keto); 52.55 ($COCH_2CO$); 57.31(NC(CH_3)$_3$ enol); 57.78 (NC(CH_3)$_3$ keto); 126.23, 126.71, 126.88, 128.42, 128.48, 128.69, 128.78, 128.89, 138.01, 138.51 (*Ar*); 167.49 (NCO keto); 173.54 (CO enol); 174.83 (CO enol); 203.30 (CH_3CO keto).

IR (neat, cm^{-1}): 2971, 1723, 1635, 1395, 702

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36; O, 12.24. Found: C, 73.24; H, 8.74; N, 5.37; O, 12.66.

5.6.3.22. **Reaction behavior of N-(*tert*-butyl)-2-(acetyl)-N-(phenylethyl)acetamide under iodine (III) mediated C-H insertion conditions**



Scheme 288

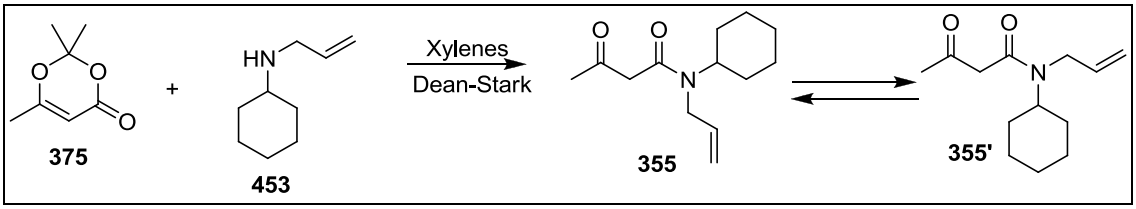
In a round bottom flask was placed (diacetoxyiodo)benzene **231** (131.2 mg, 0.407 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.8 mg, 0.620 mmol) was added followed by N-(*tert*-butyl)-2-(acetyl)-N-(phenylethyl)acetamide **376** (69.9 mg, 0.267mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4,

filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (10% AcOEt in hexanes) providing *trans*-3-acetyl-4-benzyl-1-(*tert*-butyl)-β-lactam **46** as a yellow liquid (21.9 mg, 37%).

Spectral data obtained as previously reported[39]

R_f = 0.31 (silica, 20% AcOEt in hexanes).
^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (s, 9H, NC(CH_3)$_3$), 2.07 (s, 3H, CH_3CO), 2.67 (dd, 1H, J=10.4 Hz, J=14.0 Hz, PhC*H*HC), 3.39 (dd, 1H, J=4.4 Hz, J=14.0 Hz, PhCH*H*C), 3.50 (d, 1H, J=2.0, CH_2C*H*CO), 4.30 (ddd, 1H, J=2.0 Hz, J=4.4 Hz, J=10.4 Hz, NC*H*CH_2), 7.15-7.32 (5H, m, *Ph*).
^{13}C NMR (100 MHz, $CDCl_3$): 28.43 (s, 9H, NC(CH_3)$_3$); 29.95 (CH_3CO); 40.51; 52.59; 54.64 (N*C*(CH_3)$_3$); 66.14 (CO*C*HCO); 126.98, 128.52, 128.81, 136.56 (*Ph*); 162.14 (N*C*O); 200.28 (CH_3*C*O).

5.6.3.23. **Synthesis of 2-(acetyl)-N-(allylcyclohexyl)acetamide**



Scheme 289

Prepared following general procedure[132]

In a round bottom flask, allylcyclohexylamine **453** (500 mg, 3.59 mmol) was added to 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **375** (460 mg, 3.24 mmol) in xylenes (3 mL). A dean-stark with xylenes was adapted and the mixture was heated at 120ºC with stirring for 5h. The solvent was removed under vacuum. The residue was purified through silica gel automatic chromatography (AcOEt/hexanes, gradient). 2-(acetyl)-N-(allylcyclohexyl)acetamide **355** was obtained as a brown viscous liquid (563 mg, 78%) and as a keto-enol equilibrium and rotamer mixture each (pure complex mixture).

Both ^{1}H and ^{13}C NMR spectra were too much complex to be unambiguously interpreted, even with bidimensional correlations. A description is provided instead.

R_f = 0.30 (silica, 20% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.10 (m, 1.46 H); 1.22–1.50 (m, 5.80 H); 1.61-1.82 (m, 6.95 H); 1.90-1.95 (m, 1.09); 2.02 (bs, 0.50 H); 2.23 (s, 1.69 H); 2.26 (s, 1.13 H); 3.40-3.45 (m, 1.53 H); 3.56 (s, 0.90 H); 3.79 (bs, 1.66 H); 3.89-3.93 (m, 1.10 H); 3.49 (bs, 0.83 H); 4.95 (s, 0.21 H); 5.06-5.20 (m, 2.69 H); 5.73-5.84 (m, 1.22 H); 14.83 (s, 0.17 H); 14.97 (s, 0.07 H).

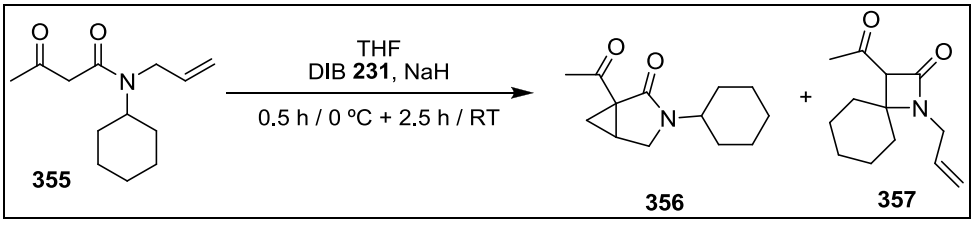
^{13}C NMR (100 MHz, $CDCl_3$): δ 21.99 (+); 25.15 (-); 25.45 (-); 25.69 (-); 25.74 (-); 25.82 (-); 30.13 (+); 30.32 (+); 30.51 (-); 30.67 (-); 31.64(-); 31.78 (-); 44.12 (-); 44.98 (-); 45.80(-); 50.35(-); 50.51 (-); 52.46 (+); 53.59 (+); 58.39 (+); 88.31 (+); 115.92 (-); 116.27(-); 116.50 (-); 134.83 (+); 134.93 (+); 135.00 (+); 165.92(q); 167.14 (q); 172.06 (q); 174.55 (q); 202.67 (q); 202.98 (q).

IR (neat, cm^{-1}): 2932, 2856, 1723, 1635, 1244, 932, 777, 718

MS (EI) *m/z*: 124, 138, 166

HMRS (EI): *m/z* calcd. $[M]^+$= 223.1572, found $[M]^+$: 223.1575.

5.6.3.24. Reaction behavior of 2-(acetyl)-N-(allylcyclohexyl)acetamide under iodine (III) mediated C-H insertion conditions



Scheme 290

In a round bottom flask was placed (diacetoxyiodo)benzene **231** (174.4 mg, 0.542 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo)benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (24.6 mg, 0.615 mmol) was added followed by 2-(acetyl)-N-(allylcyclohexyl)acetamide **355** (59.7 mg, 0.267mmol) dissolved in THF (1mL). The

flask was protected from light with aluminum foil and stirred at 0 ºC for 30 min when it was placed at room temperature (20 ºC) protected from light. After 2.5 h at room temperature NH_4Cl aq. sat. (6 mL) was added and the solution was extracted with dichloromethane (3x). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvents removed under reduced pressure. The residue was purified through neutral alumina flash chromatography (15% AcOEt in hexanes, gradient) where the products were isolated as yellow liquids, **356** (13.2 mg, 22%) and **357** (25.4mg, 43%).

356:

R_f = 0.27 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99-1.01 (m, 1H, COCCH*H*); 1.04-1.84 (m, 10H, C*H*$_2$C*H*$_2$); 1.92 (dd, J= 4.0 Hz, J= 8.4 Hz, COCC*H*H); 2.31-2.42 (m, 1H, NCH$_2$C*H*); 2.59 (s, 3H, C*H*$_3$CO); 3.25 (d, J= 10.4 Hz, 1H, NCH*H*); 3.48 (dd, J= 6.0 Hz, J= 10.4 Hz, 1H, NC*H*H); 3.83-3.90 (m, 1H, NC*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.12 (COC*C*H$_2$); 24.83 (NCH$_2$*C*H); 25.35, 25.37, 25.47 (*C*H$_2$*C*H$_2$); 29.66 (*C*H$_3$CO); 30.17, 30.50 (*C*H$_2$*C*H$_2$); 39.61 (CO*C*CO); 43.17 (N*C*H$_2$); 50.50 (N*C*H); 170.50 (N*C*O); 203.69 (CH$_3$*C*O).

IR (neat, cm^{-1}): 2932, 2856, 1694, 1442, 1316, 1218

MS (EI) *m/z*: 55, 140, 178, 221

HMRS (EI): *m/z* calcd. [M]$^+$= 221.1416, found [M]$^+$: 221.1416

357:

R_f = 0.15 (silica, 30% AcOEt in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10-1.26 (m, 2H, C*H*$_2$CH$_2$); 1.33-1.44 (m, 1H, C*H*HCH$_2$); 1.55-1.86 (m, 7H, C*H*$_2$C*H*$_2$); 2.03-2.06 (m, 1H, C*H*HCH$_2$); 2.35 (s, 3H, C*H*$_3$CO); 3.74-3.86 (m, 3H, COC*H*CO, NC*H*$_2$); 5.16-5.30 (m, 2H, C*H*$_2$CHCH$_2$N); 5.76-5.86 (m, 1H, NCH$_2$C*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.64, 24.35, 24.65, 30.54 (*C*H$_2$*C*H$_2$); 32.02 (*C*H$_3$CO); 37.21 (*C*H$_2$CH$_2$); 41.70 (N*C*H$_2$); 64.29 (N*C*CH$_2$); 69.46 (CO*C*HCO); 117.83 (*C*H$_2$CHCH$_2$N); 133.21 (NCH$_2$*C*H); 163.49 (N*C*O); 202.04 (CH$_3$*C*O).

IR (neat, cm^{-1}): 2933, 2857, 1756, 1704, 1360, 1162, 930

MS (EI) *m/z*: 123, 138, 178, 206

HMRS (EI): *m/z* calcd. $[M]^+$= 221.1416, found $[M]^+$: 221.1415

5.6.3.25. Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(dicyclohexyl)acetamide followed by ESI-LRMS^2

In a round bottom flask was placed (diacetoxyiodo)benzene (133 mg, 0.413 mmol), followed by THF (3.8 mL). The solution was stirred until no more the (diacetoxyiodo) benzene solubilized. The colorless solution was placed at 0 ºC with an ice/water bath. NaH (25 mg, 0.625 mmol) was added followed by 2-(acetyl)-N-(dicyclohexyl)acetamide **399** (71 mg, 0.268 mmol) dissolved in THF (1mL). The flask was protected from light with aluminum foil. An aliquot was filtered (PTFE) and injected. The fragmentation spectra were taken and to the main peaks ms/ms were performed. After 30 min another aliquot was taken, filtered and injected. The fragmentation spectra were taken and to the main peaks ms/ms were performed.

5.6.3.26. Iodine (III)-mediated C-H insertion on 2-(acetyl)-N-(di*iso*propyl)acetamide followed by ^{1}H NMR in THF-d_8 at 0ºC

An oven dried NMR tube was placed under Ar. 2-(Acetyl)-N-(di*iso*propyl)acetamide **311** (20.0 mg, 0.108 mmol) was added, followed by THF-d_8(previsously dried with activated sieves and degassed with Ar, 400μL). A ^{1}H NMR was traced at 0ºC. (Diacetoxyiodo)benzene (51.8 mg, 0.155 mmol) was added and another ^{1}H NMR was traced at 0 ºC.

Then NaH (10.7 mg, 0.268 mmol) was added, the solution become very opaque and with H_2 bubbles which prevented the spectra acquisition. Afterwards another ^{1}H NMR to the opaque and viscous reaction mixture revealed only product peaks and iodobenzene as well as some remaining substrate. The iodonium intermediate was not detected in this experiment.

Due to the high concentration DIB was not completely soluble all over the experiment.

6. APPENDIX

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **118** (Scheme 58). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	2059(1)	1281(1)	1752(1)	13(1)
C(2)	1853(1)	2560(1)	1507(1)	14(1)
C(3)	3055(1)	2578(1)	1026(1)	13(1)
C(4)	3230(1)	1057(1)	1303(1)	13(1)
C(5)	1236(1)	401(1)	2221(1)	15(1)
C(6)	-4(1)	204(2)	1758(1)	24(1)
C(7)	1011(2)	1103(2)	3006(1)	25(1)
C(8)	1874(1)	-959(1)	2369(1)	24(1)
O(9)	1027(1)	3372(1)	1624(1)	19(1)
S(10)	2819(1)	2869(1)	-9(1)	14(1)
O(11)	1641(1)	2264(1)	-251(1)	21(1)
O(12)	3946(1)	2457(1)	-391(1)	22(1)
C(13)	2678(1)	4638(1)	-115(1)	15(1)
C(14)	3571(1)	5317(1)	-542(1)	18(1)
C(15)	3374(1)	6671(1)	-719(1)	22(1)
C(16)	2308(1)	7320(1)	-467(1)	21(1)
C(17)	1438(1)	6641(1)	-22(1)	22(1)
C(18)	1613(1)	5287(1)	155(1)	20(1)
C(19)	3071(1)	-18(1)	664(1)	17(1)
C(20)	4412(1)	882(1)	1823(1)	13(1)
C(21)	4543(1)	1557(1)	2544(1)	17(1)
C(22)	5646(1)	1459(1)	3003(1)	20(1)
C(23)	6643(1)	686(1)	2743(1)	22(1)
C(24)	6517(1)	4(1)	2032(1)	22(1)
C(25)	5412(1)	96(1)	1575(1)	17(1)

Atomic coordinates (x, y, z) for all optimized structures by DFT

Scheme 56: $Rh_2(OAc)_4$ **1**

45	0.901743000	0.578993000	-0.508676000
45	-0.878547000	-0.655646000	0.492144000
8	1.807160000	0.657216000	1.342966000
1	1.270672000	-0.044018000	4.477095000
1	-1.508016000	0.466603000	-4.380684000
6	1.234309000	0.093185000	2.331015000
8	-1.786424000	-0.729102000	-1.358793000
6	-1.208634000	-0.173803000	-2.349031000
8	-0.092640000	0.438383000	-2.313236000
8	0.116726000	-0.516413000	2.295967000
6	1.963712000	0.128636000	3.653288000
6	-1.902584000	-0.276080000	-3.686986000
1	2.477406000	1.084468000	3.771706000
1	-1.730561000	-1.275678000	-4.099808000
8	1.849993000	-1.213512000	-0.892165000
8	-1.824938000	1.135536000	0.879423000
6	1.277047000	-2.296348000	-0.544279000
6	-1.254533000	2.218141000	0.527530000
1	2.720919000	-0.662765000	3.658256000
1	-2.979443000	-0.150445000	-3.557196000
8	-0.132098000	2.309687000	-0.068320000
8	0.154329000	-2.388075000	0.050287000
6	1.975871000	-3.588957000	-0.894643000
6	-1.960601000	3.513390000	0.852673000
1	1.785212000	-4.340259000	-0.126448000
1	-2.041829000	4.123179000	-0.050816000
1	3.046508000	-3.421400000	-1.016897000
1	-2.948915000	3.318179000	1.268345000
1	1.570961000	-3.962350000	-1.841487000
1	-1.361348000	4.075715000	1.575284000

Scheme 56: $Rh_2(tfa)_4$ **102**

45	0.905303000	0.588545000	-0.495044000
45	-0.883078000	-0.655181000	0.493603000
8	1.799513000	0.653721000	1.353427000
9	1.129040000	-0.120574000	4.682187000
9	-1.427859000	0.645169000	-4.543223000
6	1.206789000	0.084202000	2.313160000
8	-1.778717000	-0.716829000	-1.354047000
6	-1.181862000	-0.154845000	-2.315904000
8	-0.077321000	0.457482000	-2.297390000
8	0.100801000	-0.525744000	2.295429000
6	1.961393000	0.101947000	3.662611000
6	-1.882942000	-0.274010000	-3.689064000
9	2.568201000	1.279831000	3.844076000
9	-1.638510000	-1.495315000	-4.193988000
8	1.849984000	-1.195007000	-0.884761000
6	1.262974000	-2.257094000	-0.534552000
9	2.894112000	-0.866337000	3.644595000
9	-3.205006000	-0.122568000	-3.550236000
8	0.148452000	-2.376224000	0.049403000
6	1.967650000	-3.583896000	-0.900563000
9	1.827281000	-4.474447000	0.087644000
9	3.268214000	-3.389698000	-1.129777000
9	1.400357000	-4.080039000	-2.013631000
8	-1.828264000	1.128318000	0.884975000
6	-1.242701000	2.189572000	0.531278000
8	-0.126965000	2.309137000	-0.050704000
6	-1.965456000	3.522086000	0.836389000
9	-2.211427000	4.167279000	-0.313995000
9	-3.119723000	3.314968000	1.471834000
9	-1.178779000	4.292011000	1.602784000

Scheme 56: $Rh_2(cap)_4$ **35**

45	-0.608589000	-0.693349000	-0.699192000
45	0.520430000	0.748585000	0.841073000
8	-0.751343000	0.903115000	-2.029639000
8	-2.414450000	-0.138097000	0.177219000
8	2.326288000	0.193314000	-0.035320000
8	0.663189000	-0.847880000	2.171518000
7	1.215423000	-1.150255000	-1.519209000
7	0.349486000	2.253996000	-0.543560000
7	-1.303588000	1.205511000	1.661078000
7	-0.437640000	-2.198763000	0.685440000
6	2.314774000	-0.598031000	-1.047400000
6	-0.244916000	2.038057000	-1.698874000
6	-2.402935000	0.653261000	1.189286000
6	0.156769000	-1.982824000	1.840751000
6	0.310005000	-3.083547000	2.882272000
6	3.671193000	-0.831655000	-1.698561000
6	-0.398126000	3.138772000	-2.740407000
6	-3.759349000	0.886870000	1.840464000
6	1.205040000	-4.254695000	2.428370000
6	3.790710000	-0.197983000	-3.100522000
6	-1.293139000	4.309946000	-2.286531000
6	-3.878838000	0.253202000	3.242430000
6	0.519078000	-5.243693000	1.475259000
6	3.095118000	-0.993123000	-4.214658000
6	-0.607166000	5.298940000	-1.333424000
6	-3.183244000	1.048360000	4.356554000

6	1.589631000	-1.222383000	-4.018219000
6	-0.089917000	4.691330000	-0.022369000
6	-1.677765000	1.277647000	4.160091000
6	0.001797000	-4.636082000	0.164217000
6	1.231120000	-1.978419000	-2.726498000
6	0.931548000	3.555482000	-0.211602000
6	-1.319289000	2.033682000	2.868359000
6	-1.019686000	-3.500256000	0.353482000
1	4.411159000	-0.396069000	-1.023949000
1	-0.826127000	2.661090000	-3.624154000
1	-4.499319000	0.451271000	1.165865000
1	0.738005000	-2.605867000	3.766021000
1	-0.680484000	-3.466743000	3.164746000
1	-3.966288000	1.963666000	1.904433000
1	0.592374000	3.521945000	-3.022876000
1	3.878118000	-1.908454000	-1.762532000
1	-2.201922000	3.904894000	-1.823052000
1	3.395511000	0.825442000	-3.062665000
1	-3.483620000	-0.770216000	3.204573000
1	2.113808000	-3.849617000	1.964887000
1	-1.620585000	4.858189000	-3.178167000
1	4.855070000	-0.107979000	-3.349511000
1	-4.943192000	0.163180000	3.491433000
1	1.532508000	-4.802943000	3.319995000
1	3.259328000	-0.483523000	-5.172554000
1	-1.303604000	6.114703000	-1.101950000
1	-3.347431000	0.538759000	5.314454000
1	1.215533000	-6.059437000	1.243768000
1	3.588553000	-1.972397000	-4.303349000
1	0.239436000	5.762522000	-1.861147000
1	-3.676696000	2.027624000	4.445248000
1	-0.327506000	-5.707302000	2.002987000
1	1.213232000	-1.800451000	-4.872477000
1	0.384322000	5.487327000	0.566887000
1	-1.301363000	1.855727000	5.014340000
1	-0.472435000	-5.432084000	-0.425038000
1	1.045166000	-0.270700000	-4.013203000
1	-0.924999000	4.307625000	0.576760000
1	-1.133283000	0.325973000	4.155072000
1	0.836862000	-4.252354000	-0.434921000
1	0.223773000	-2.396235000	-2.832905000
1	1.487990000	3.421132000	0.722667000
1	-0.311953000	2.451527000	2.974750000
1	-1.576154000	-3.365906000	-0.580772000
1	1.903432000	-2.842022000	-2.601096000
1	1.680375000	3.852420000	-0.962100000
1	-1.768490000	-3.797215000	1.103995000
1	-1.991626000	2.897267000	2.742961000

Scheme 56: $Rh_2(OAc)_4(IPr)$ **88**

45	1.337922000	-1.780604000	-3.248755000
45	0.308327000	-0.758991000	-1.267396000
6	-0.538207000	0.135680000	0.516788000
7	-0.814709000	-0.466039000	1.720584000
8	0.247607000	-2.685201000	-0.485005000
8	1.403340000	0.080846000	-4.121258000
1	1.096218000	3.217386000	-3.479196000
7	-0.848609000	1.453093000	0.747199000
1	-0.068117000	2.554965000	-4.628790000
8	0.464068000	1.046746000	-2.292874000
6	-1.300363000	1.655840000	2.048436000
8	1.224912000	-3.611641000	-2.312785000
1	-1.591254000	2.632127000	2.399922000
1	-1.551069000	0.150193000	3.657188000
8	-1.533827000	-1.104273000	-2.175095000
6	-1.279813000	0.451707000	2.658753000
8	3.177796000	-1.433521000	-2.372455000
1	1.665362000	2.417647000	-4.986563000
8	2.235902000	-0.491745000	-0.530471000
8	-0.567690000	-2.057569000	-3.999087000
6	0.941115000	1.068544000	-3.477143000
6	0.709033000	-3.667661000	-1.158115000
6	-0.718699000	-1.859086000	2.110660000
1	1.101321000	-5.782807000	-1.124714000
1	-0.437241000	-5.290942000	-0.360034000
1	3.812571000	-1.407164000	2.547816000
1	3.216035000	-2.970694000	3.107449000
6	0.452517000	-2.300148000	2.754945000
1	2.881890000	-2.436880000	1.446881000
1	0.907670000	-0.370429000	4.716170000
1	2.663900000	-0.266211000	4.516054000
1	1.923461000	-1.770355000	5.085916000
1	1.344838000	-3.975561000	3.767969000
6	0.460305000	-3.607674000	3.257118000
1	1.075386000	-4.996022000	0.486728000
6	-0.647150000	-4.440046000	3.120157000
1	-0.621586000	-5.448764000	3.523221000
1	-2.878031000	-2.105183000	-4.965617000
1	-2.645981000	-4.634942000	2.363638000
6	-1.786722000	-3.979212000	2.467938000
1	-3.636219000	-1.173306000	-3.631951000
1	1.553297000	-0.530595000	2.301342000
6	-1.850546000	-2.679689000	1.950336000
1	-3.315187000	-2.901453000	-3.440937000
1	-5.191538000	-1.716846000	1.760258000
1	-4.052304000	-1.404013000	3.080533000
1	-4.385550000	-2.716064000	-0.435688000
1	-3.726593000	-4.131402000	0.392241000
1	-2.678463000	-3.143419000	-0.651035000

6	0.615374000	-5.029956000	-0.503967000
6	0.923253000	2.405764000	-4.187251000
1	4.572518000	0.056900000	0.175805000
6	-0.791660000	2.589915000	-0.150008000
1	5.278623000	-0.269909000	-1.439608000
6	-1.951639000	2.933613000	-0.868845000
1	5.012127000	-1.598335000	-0.308691000
1	-3.000416000	1.157099000	-0.318507000
1	-2.803290000	4.416194000	-2.176241000
1	-2.939430000	-1.209362000	0.851034000
6	-1.922923000	4.119289000	-1.614306000
1	-0.794706000	5.851551000	-2.209550000
6	-0.792096000	4.929517000	-1.634665000
1	-4.579728000	1.064862000	-2.186260000
1	1.218862000	5.201275000	-0.937419000
6	0.342278000	4.560819000	-0.915930000
1	1.515354000	1.985611000	0.976810000
1	-4.536276000	-3.062300000	2.704202000
6	0.371710000	3.382182000	-0.160860000
1	3.755092000	2.711529000	0.330755000
6	3.229318000	-0.870603000	-1.240135000
6	-1.564506000	-1.682701000	-3.314907000
6	-2.938265000	-1.973458000	-3.884641000
6	4.610580000	-0.642209000	-0.659697000
1	3.112521000	4.059106000	-0.609612000
1	2.774099000	2.388645000	-1.109911000
1	2.671105000	3.637521000	2.440705000
1	0.915677000	3.851032000	2.530834000
1	1.893908000	4.972760000	1.575681000
1	-2.915052000	1.180910000	-2.785841000
1	-3.987674000	2.597471000	-2.833143000
6	1.676304000	-1.408483000	2.940139000
1	-5.237938000	2.184801000	0.002629000
6	1.796718000	-0.925514000	4.399725000
1	-4.615373000	3.757918000	-0.518734000
6	2.970569000	-2.104421000	2.483493000
1	-4.026877000	3.029368000	0.981270000
6	-3.125269000	-2.205553000	1.260291000
6	-3.497419000	-3.109456000	0.070660000
6	-4.291948000	-2.090309000	2.261544000
6	-3.224883000	2.093783000	-0.834820000
6	-3.701074000	1.716402000	-2.249021000
6	-4.339259000	2.809457000	-0.044955000
6	1.624458000	3.015530000	0.628521000
6	2.888824000	3.049519000	-0.248041000
6	1.782803000	3.922005000	1.865993000

Scheme 56: $Rh_2(OAc)_4(SIPr)$ **89**

45	2.783736000	-2.344592000	1.445895000
45	1.028581000	-4.016422000	1.872909000
8	3.726253000	-3.132347000	3.124151000
6	3.190760000	-4.088618000	3.778466000
8	0.020406000	-3.311120000	0.224013000
6	0.518888000	-2.345250000	-0.424949000
8	1.625660000	-1.758474000	-0.178797000
8	2.093635000	-4.660735000	3.510390000
6	3.935351000	-4.557263000	5.010104000
6	-0.274255000	-1.814536000	-1.600173000
8	3.711353000	-3.782051000	0.256652000
6	3.164586000	-4.930553000	0.129576000
8	2.090294000	-5.318627000	0.673397000
6	3.857481000	-5.915543000	-0.789787000
6	4.349280000	-0.871574000	1.065347000
7	4.374732000	0.037241000	0.059535000
7	5.491873000	-0.707964000	1.776889000
6	6.349169000	0.395223000	1.280845000
6	5.611199000	0.854575000	0.027108000
6	3.431596000	0.327126000	-0.992680000
6	2.492982000	1.362287000	-0.795922000
6	1.689241000	1.737904000	-1.879283000
6	1.817839000	1.123450000	-3.120624000
6	2.755115000	0.109772000	-3.295529000
6	3.579931000	-0.307979000	-2.243910000
6	5.990837000	-1.375379000	2.954565000
6	6.893823000	-2.448037000	2.797080000
6	7.495503000	-2.976595000	3.945925000
6	7.222931000	-2.457305000	5.207872000
6	6.332298000	-1.396626000	5.340479000
6	5.703169000	-0.831655000	4.224615000
6	2.330670000	2.091097000	0.534386000
6	2.715676000	3.579729000	0.416059000
6	0.902863000	1.938186000	1.090922000
6	4.597672000	-1.415882000	-2.495246000
6	3.919094000	-2.702335000	-3.001284000
6	5.699199000	-0.961449000	-3.474719000
6	7.247093000	-3.038329000	1.435724000
6	6.928421000	-4.543408000	1.371475000
6	8.723307000	-2.778283000	1.071766000
6	4.750949000	0.342706000	4.426302000
6	3.585412000	-0.028528000	5.361792000
6	5.492344000	1.590151000	4.949356000
1	3.730300000	-3.863114000	5.832061000
1	5.011214000	-4.542673000	4.828300000
1	3.599288000	-5.553916000	5.298433000
1	-1.093500000	-2.492176000	-1.841502000
1	-0.679427000	-0.830885000	-1.342359000
1	0.381732000	-1.676501000	-2.462224000
1	4.919336000	-5.684060000	-0.878238000
1	3.402347000	-5.848632000	-1.783786000

1	3.713748000	-6.932839000	-0.421430000
1	7.357288000	0.024836000	1.076023000
1	6.424764000	1.177425000	2.043305000
1	5.358934000	1.918529000	0.040256000
1	6.166257000	0.650527000	-0.894380000
1	0.958795000	2.531047000	-1.749400000
1	1.191468000	1.436265000	-3.951579000
1	2.853756000	-0.363828000	-4.267864000
1	8.194993000	-3.801639000	3.847517000
1	7.706802000	-2.876120000	6.086011000
1	6.125353000	-0.993761000	6.327652000
1	3.004460000	1.625844000	1.259112000
1	3.737651000	3.709807000	0.043669000
1	2.646560000	4.072266000	1.392265000
1	2.047911000	4.110849000	-0.270934000
1	0.824511000	2.422784000	2.070349000
1	0.162019000	2.403486000	0.431281000
1	0.653116000	0.882418000	1.210697000
1	5.070451000	-1.663888000	-1.541045000
1	4.658036000	-3.504586000	-3.102134000
1	3.455930000	-2.555294000	-3.983262000
1	3.151441000	-3.028961000	-2.297803000
1	6.449282000	-1.749776000	-3.601821000
1	6.212405000	-0.059542000	-3.124303000
1	5.283324000	-0.736569000	-4.463051000
1	6.621459000	-2.549226000	0.684211000
1	7.135591000	-4.929926000	0.367367000
1	5.875887000	-4.721096000	1.598932000
1	7.540340000	-5.116966000	2.076373000
1	8.943706000	-3.159648000	0.068665000
1	9.399566000	-3.279205000	1.773149000
1	8.967977000	-1.710719000	1.088765000
1	4.310842000	0.591191000	3.456664000
1	2.886131000	0.810925000	5.443935000
1	3.938040000	-0.262539000	6.372326000
1	3.042841000	-0.891203000	4.971348000
1	4.802889000	2.436920000	5.038364000
1	6.311147000	1.889446000	4.286123000
1	5.924530000	1.409158000	5.939600000
8	0.075936000	-2.612389000	3.051717000
6	0.591511000	-1.464412000	3.183054000
8	1.684092000	-1.055311000	2.660463000
6	-0.178596000	-0.462427000	4.019085000
1	0.491788000	0.286755000	4.441805000
1	-0.906725000	0.046567000	3.378295000
1	-0.726875000	-0.979295000	4.808516000

Scheme 56: $Rh_2(OAc)_4{}^{Cl}(IPr)$ **91**

45	1.324385000	-1.764287000	-3.232214000
45	0.304032000	-0.748612000	-1.246854000
6	-0.551345000	0.158408000	0.565010000
7	-0.835580000	-0.456659000	1.764051000
8	0.269957000	-2.674603000	-0.461346000
8	1.376289000	0.092570000	-4.109654000
7	-0.863792000	1.480647000	0.786032000
8	0.431918000	1.053388000	-2.282042000
6	-1.329715000	1.673424000	2.087460000
8	1.228016000	-3.595698000	-2.301280000
17	-1.822065000	3.181684000	2.733863000
17	-1.794268000	0.076106000	4.294382000
8	-1.539778000	-1.118187000	-2.142095000
6	-1.313905000	0.465112000	2.696669000
8	3.168810000	-1.412210000	-2.376074000
8	2.237027000	-0.465150000	-0.532883000
8	-0.578054000	-2.055770000	-3.975351000
6	0.907530000	1.078435000	-3.466909000
6	0.724759000	-3.655708000	-1.140829000
6	-0.731815000	-1.859471000	2.129073000
6	0.444177000	-2.309026000	2.759839000
6	0.457032000	-3.628089000	3.230526000
6	-0.646554000	-4.461661000	3.077093000
6	-1.788686000	-3.991657000	2.436844000
6	-1.861609000	-2.680459000	1.951646000
6	0.640800000	-5.019815000	-0.490649000
6	0.882829000	2.415542000	-4.175558000
6	-0.791779000	2.607032000	-0.129003000
6	-1.937534000	2.932945000	-0.879948000
6	-1.891879000	4.102475000	-1.648866000
6	-0.762127000	4.913916000	-1.661472000
6	0.356379000	4.561496000	-0.912016000
6	0.371052000	3.400743000	-0.129249000
6	3.227489000	-0.843592000	-1.246549000
6	-1.574471000	-1.694475000	-3.282970000
6	-2.948299000	-1.999099000	-3.843472000
6	4.612291000	-0.606807000	-0.679663000
6	1.679393000	-1.435105000	2.957953000
6	1.893602000	-1.081317000	4.443691000
6	2.938495000	-2.102065000	2.373822000
6	-3.143944000	-2.207378000	1.273851000
6	-3.474327000	-3.065546000	0.038157000
6	-4.328266000	-2.179980000	2.260804000
6	-3.211844000	2.093210000	-0.875026000
6	-3.604238000	1.655777000	-2.298398000
6	-4.375669000	2.837431000	-0.189602000
6	1.619666000	3.061340000	0.679250000
6	2.861400000	2.953645000	-0.225698000
6	1.854937000	4.081332000	1.811410000
1	1.344432000	-4.003134000	3.731100000
1	-0.615992000	-5.478997000	3.457438000
1	-2.644784000	-4.648890000	2.318415000

1	1.119227000	-5.769778000	-1.120588000
1	-0.409650000	-5.281722000	-0.333706000
1	1.113795000	-4.988989000	0.493896000
1	1.136918000	3.217500000	-3.480559000
1	-0.133489000	2.603973000	-4.537593000
1	1.564887000	2.404722000	-5.026313000
1	-2.759852000	4.386354000	-2.235997000
1	-0.753566000	5.824008000	-2.254976000
1	1.233429000	5.201416000	-0.928247000
1	-2.890317000	-2.151313000	-4.921769000
1	-3.646893000	-1.195357000	-3.604556000
1	-3.322762000	-2.918178000	-3.379840000
1	4.575720000	0.074060000	0.170514000
1	5.263475000	-0.207596000	-1.460733000
1	5.033207000	-1.564276000	-0.356407000
1	1.531168000	-0.503057000	2.406056000
1	1.030062000	-0.561835000	4.868006000
1	2.769645000	-0.433260000	4.556427000
1	2.067428000	-1.982201000	5.042673000
1	3.791976000	-1.420077000	2.448887000
1	3.201663000	-3.016872000	2.915876000
1	2.790049000	-2.350548000	1.321539000
1	-2.985890000	-1.186453000	0.915740000
1	-4.366921000	-2.673969000	-0.461664000
1	-3.679714000	-4.105869000	0.313659000
1	-2.646409000	-3.046469000	-0.673089000
1	-5.227311000	-1.799227000	1.764135000
1	-4.120208000	-1.541746000	3.124550000
1	-4.556804000	-3.183671000	2.635640000
1	-3.018815000	1.179817000	-0.305847000
1	-4.483268000	1.002965000	-2.258800000
1	-2.787959000	1.105168000	-2.769527000
1	-3.861297000	2.513673000	-2.928936000
1	-5.268282000	2.202982000	-0.162732000
1	-4.634833000	3.752646000	-0.733104000
1	-4.127653000	3.119436000	0.837559000
1	1.475405000	2.078333000	1.135603000
1	3.729221000	2.639187000	0.363982000
1	3.109994000	3.916005000	-0.686581000
1	2.698716000	2.219828000	-1.016948000
1	2.733279000	3.798328000	2.401784000
1	0.996797000	4.143108000	2.486546000
1	2.035152000	5.084144000	1.408530000

Scheme 60:Metal-carbenoid between **1** and **69**

45	1.995478000	0.995800000	0.021499000
45	-0.302439000	0.351467000	0.591259000
8	2.515373000	0.512603000	1.965087000
6	1.633575000	0.083765000	2.761783000
8	-0.800811000	0.824662000	-1.360235000
6	0.093386000	1.296242000	-2.143417000
8	1.316177000	1.467685000	-1.870043000
8	0.398951000	-0.121955000	2.490558000
6	2.058850000	-0.189558000	4.188730000
6	-0.376712000	1.673240000	-3.531707000
8	-0.563468000	2.305277000	1.181942000
6	0.387575000	3.149357000	1.064377000
8	1.554050000	2.911542000	0.630778000
6	0.061253000	4.567040000	1.477358000
6	-2.197053000	-0.128992000	1.100714000
6	-2.553619000	-0.659163000	2.407770000
7	-2.614831000	-1.912327000	2.866226000
8	-2.779749000	0.426547000	2.993741000
6	-2.988695000	-2.132888000	4.325639000
6	-3.219166000	-3.620223000	4.640537000
6	-1.850116000	-1.588679000	5.210805000
6	-4.314309000	-1.399587000	4.626925000
6	-2.117238000	-2.969363000	1.932163000
6	-3.179408000	-4.017882000	1.595415000
6	-4.471468000	-3.603539000	1.233740000
6	-5.442730000	-4.535452000	0.871496000
6	-5.141240000	-5.899607000	0.853936000
6	-3.858174000	-6.320435000	1.199478000
6	-2.885503000	-5.386303000	1.566396000
15	-3.641005000	0.372054000	0.080894000
8	-4.951195000	0.033898000	0.972550000
6	-5.682041000	1.114462000	1.619614000
6	-6.822054000	1.594518000	0.738814000
8	-3.612579000	1.732803000	-0.503443000
8	-3.647912000	-0.895070000	-0.913525000
6	-3.483862000	-0.751727000	-2.352716000
6	-2.540991000	-1.835216000	-2.839388000
6	-0.741352000	-3.508228000	2.347381000
1	1.831269000	0.692243000	4.797354000
1	3.132650000	-0.374909000	4.233199000
1	1.503196000	-1.033704000	4.600982000
1	-0.719585000	0.776456000	-4.057071000
1	-1.225562000	2.357907000	-3.454022000
1	0.433526000	2.137350000	-4.093890000
1	0.965349000	5.175914000	1.494292000
1	-0.653298000	4.989251000	0.763958000
1	-0.418109000	4.564838000	2.459303000
1	-3.447092000	-3.693162000	5.708130000
1	-4.063362000	-4.032726000	4.087196000
1	-2.344294000	-4.243483000	4.454998000
1	-2.133404000	-1.671845000	6.265225000
1	-1.645628000	-0.540112000	4.987825000
1	-0.931607000	-2.163085000	5.059890000
1	-4.625827000	-1.641852000	5.647706000
1	-5.098942000	-1.736458000	3.942927000

1	-4.215463000	-0.318024000	4.545157000
1	-1.932827000	-2.425048000	0.997966000
1	-4.721325000	-2.547410000	1.234894000
1	-6.436442000	-4.193273000	0.596329000
1	-5.898473000	-6.624896000	0.570396000
1	-3.608625000	-7.377749000	1.188164000
1	-1.895450000	-5.738239000	1.835720000
1	-6.047178000	0.685102000	2.556030000
1	-4.995477000	1.929834000	1.859183000
1	-7.410212000	2.349617000	1.272052000
1	-7.484800000	0.765447000	0.473144000
1	-6.429514000	2.044048000	-0.176533000
1	-3.100798000	0.247250000	-2.567222000
1	-4.480098000	-0.855219000	-2.795701000
1	-2.437051000	-1.773199000	-3.928380000
1	-2.925974000	-2.827926000	-2.588044000
1	-1.557220000	-1.710761000	-2.380308000
1	-0.319254000	-4.092343000	1.525731000
1	-0.772321000	-4.144619000	3.234403000
1	-0.073894000	-2.665989000	2.534289000
8	2.328354000	-0.956732000	-0.572783000
6	1.382400000	-1.791042000	-0.504968000
8	0.194824000	-1.560691000	-0.084218000
6	1.676769000	-3.213488000	-0.933341000
1	1.989961000	-3.789635000	-0.055724000
1	2.491277000	-3.225386000	-1.658755000
1	0.783281000	-3.682519000	-1.349073000

Scheme 61:Metal-carbenoid between **89** and **69**

45	2.080132000	1.011183000	-0.005225000
45	-0.265291000	0.362049000	0.571588000
8	2.541605000	0.501260000	1.965060000
6	1.652040000	0.056476000	2.748139000
8	-0.777855000	0.860739000	-1.366451000
6	0.110953000	1.311520000	-2.158210000
8	1.341213000	1.468879000	-1.898142000
8	0.425795000	-0.144659000	2.464064000
6	2.069406000	-0.240194000	4.174140000
6	-0.366685000	1.686005000	-3.546430000
8	-0.504541000	2.314699000	1.189247000
6	0.436976000	3.158352000	1.078840000
8	1.606249000	2.931941000	0.632956000
6	0.110916000	4.575006000	1.504151000
6	-2.236811000	-0.127642000	1.108501000
6	-2.598648000	-0.643931000	2.411632000
7	-2.646709000	-1.901393000	2.876323000
8	-2.827108000	0.435931000	3.010491000
6	-2.997903000	-2.124085000	4.336957000
6	-3.212453000	-3.613575000	4.654984000
6	-1.855313000	-1.570336000	5.211609000
6	-4.326638000	-1.403258000	4.656461000
6	-2.140522000	-2.949456000	1.941138000
6	-3.190229000	-4.011110000	1.605266000
6	-4.490497000	-3.612242000	1.255165000
6	-5.452082000	-4.554998000	0.895384000
6	-5.133565000	-5.915292000	0.869487000
6	-3.842754000	-6.320919000	1.203914000
6	-2.879524000	-5.375654000	1.567708000
15	-3.678545000	0.365225000	0.101554000
8	-5.008161000	0.025121000	0.972819000
6	-5.752758000	1.103935000	1.598726000
6	-6.892767000	1.560620000	0.704376000
8	-3.658717000	1.726926000	-0.485298000
8	-3.690915000	-0.898503000	-0.904028000
6	-3.458798000	-0.746718000	-2.330655000
6	-2.514552000	-1.842959000	-2.786839000
6	-0.754812000	-3.473070000	2.344712000
1	1.874528000	0.646841000	4.786818000
1	3.135476000	-0.462824000	4.220627000
1	1.478571000	-1.063429000	4.579785000
1	-0.749131000	0.792637000	-4.050291000
1	-1.195266000	2.394716000	-3.461419000
1	0.444668000	2.117858000	-4.131035000
1	1.023672000	5.141952000	1.689783000
1	-0.454302000	5.061546000	0.702357000
1	-0.522298000	4.558963000	2.393384000
1	-3.431196000	-3.689190000	5.724469000
1	-4.057274000	-4.033650000	4.108001000
1	-2.333680000	-4.229259000	4.461708000
1	-2.125844000	-1.655390000	6.269542000
1	-1.663274000	-0.520391000	4.984260000
1	-0.933038000	-2.135912000	5.050227000
1	-4.622047000	-1.644434000	5.682598000
1	-5.117157000	-1.749626000	3.983957000
1	-4.238304000	-0.321484000	4.567081000
1	-1.967617000	-2.400642000	1.006910000
1	-4.752944000	-2.559151000	1.263694000
1	-6.452017000	-4.224205000	0.628662000
1	-5.883625000	-6.649054000	0.588227000
1	-3.579719000	-7.375038000	1.186490000
1	-1.882956000	-5.715543000	1.828635000
1	-6.121144000	0.686595000	2.539808000
1	-5.078573000	1.931853000	1.830868000
1	-7.493803000	2.316301000	1.222635000
1	-7.543912000	0.720448000	0.444362000
1	-6.497878000	2.001550000	-0.214212000
1	-3.047385000	0.245920000	-2.520791000
1	-4.435507000	-0.828277000	-2.820287000
1	-2.363660000	-1.774753000	-3.870233000
1	-2.926582000	-2.830910000	-2.559947000

1	-1.548968000	-1.738557000	-2.285928000
1	-0.329099000	-4.047969000	1.518144000
1	-0.771874000	-4.113703000	3.229340000
1	-0.099143000	-2.621586000	2.531439000
8	2.367263000	-0.966962000	-0.606804000
6	1.403657000	-1.788370000	-0.548471000
8	0.225069000	-1.544280000	-0.133020000
6	1.681441000	-3.212764000	-0.988733000
1	2.009070000	-3.793895000	-0.119686000
1	2.479365000	-3.232053000	-1.732091000
1	0.775004000	-3.673245000	-1.385439000
6	4.315508000	1.663995000	-0.534880000
7	4.743799000	2.221347000	-1.693344000
7	5.396117000	1.604550000	0.281613000
6	6.634468000	2.181265000	-0.300835000
6	6.195140000	2.534117000	-1.720851000
6	4.024948000	2.474984000	-2.914504000
6	3.501797000	3.765525000	-3.143566000
6	2.934030000	4.036091000	-4.394728000
6	2.892454000	3.067422000	-5.393053000
6	3.412630000	1.800044000	-5.147732000
6	3.989268000	1.478027000	-3.913264000
6	5.506791000	1.092660000	1.622089000
6	5.894454000	-0.251311000	1.811143000
6	6.119139000	-0.696864000	3.119854000
6	5.985640000	0.161438000	4.207088000
6	5.614499000	1.486676000	3.999331000
6	5.369800000	1.979174000	2.712138000
6	3.543903000	4.869380000	-2.092027000
6	4.457011000	6.033344000	-2.528770000
6	2.131853000	5.380798000	-1.752613000
6	4.562681000	0.080096000	-3.704914000
6	3.497113000	-1.009114000	-3.927781000
6	5.790868000	-0.166870000	-4.604830000
6	6.106018000	-1.219766000	0.651871000
6	5.189042000	-2.451840000	0.761951000
6	7.584204000	-1.645234000	0.537545000
6	4.981639000	3.443926000	2.538666000
6	3.693265000	3.784792000	3.310106000
6	6.131247000	4.385381000	2.952262000
1	7.446181000	1.448323000	-0.269836000
1	6.948100000	3.056744000	0.277809000
1	6.351811000	3.587370000	-1.971253000
1	6.693451000	1.928111000	-2.485277000
1	2.524668000	5.022834000	-4.590762000
1	2.457104000	3.300321000	-6.361177000
1	3.376339000	1.047245000	-5.929944000
1	6.416630000	-1.728260000	3.286783000
1	6.176863000	-0.200068000	5.214002000
1	5.514804000	2.153250000	4.851124000
1	3.956610000	4.441322000	-1.174499000
1	5.473929000	5.693456000	-2.753393000
1	4.519674000	6.788884000	-1.737848000
1	4.070820000	6.526020000	-3.427899000
1	2.183198000	6.131902000	-0.956430000
1	1.653933000	5.850945000	-2.619203000
1	1.502053000	4.558987000	-1.407741000
1	4.883677000	0.000107000	-2.662818000
1	3.918059000	-1.997917000	-3.712443000
1	3.143338000	-1.021423000	-4.964792000
1	2.642262000	-0.846904000	-3.268974000
1	6.225055000	-1.151971000	-4.400908000
1	6.570704000	0.586077000	-4.447946000
1	5.517557000	-0.137826000	-5.665486000
1	5.834141000	-0.701614000	-0.271743000
1	5.334761000	-3.109173000	-0.102814000
1	4.141469000	-2.145971000	0.786171000
1	5.407669000	-3.037691000	1.661901000
1	7.730697000	-2.293313000	-0.333694000
1	7.908324000	-2.202175000	1.423583000
1	8.249875000	-0.781666000	0.432540000
1	4.770298000	3.611312000	1.479103000
1	3.406967000	4.826354000	3.125962000
1	3.828324000	3.667177000	4.391232000
1	2.874004000	3.140567000	2.986992000
1	5.858746000	5.429703000	2.763833000
1	7.053322000	4.171125000	2.401188000
1	6.359058000	4.289900000	4.019756000

Scheme 168: Phenyliodonium **314**

6	2.798686000	2.415611000	-2.827982000
53	-0.393857000	2.128069000	-2.208684000
1	2.267471000	2.366072000	-3.782444000
6	2.483418000	1.228004000	-1.926520000
1	3.873930000	2.408721000	-3.006308000
7	1.199623000	-1.248731000	-0.371003000
6	1.120279000	0.823188000	-1.679319000
8	3.419303000	0.604615000	-1.421551000
1	2.530813000	3.358676000	-2.338109000
8	-0.184347000	0.431675000	0.261295000
6	-0.316768000	3.799647000	-0.866797000
1	1.413381000	-2.955905000	0.737992000
6	-0.174394000	5.072249000	-1.411570000
1	2.139947000	-1.220685000	-2.205985000
1	-0.094322000	5.220681000	-2.484471000
6	-0.128349000	6.162766000	-0.542634000
1	1.747604000	-3.581849000	-2.800176000
6	-0.211655000	5.962283000	0.834095000
1	-0.018193000	7.164312000	-0.945992000

1	0.221673000	-2.773431000	-2.383636000
6	-0.341222000	4.673743000	1.351839000
1	-0.170610000	6.813427000	1.506142000
1	0.990250000	-3.887941000	-1.233607000
6	-0.398569000	3.568065000	0.502062000
1	-0.400258000	4.521134000	2.424785000
1	-0.487546000	2.552888000	0.879683000
6	0.672480000	-0.008044000	-0.525487000
6	0.857508000	-2.019679000	0.840922000
1	-0.969012000	-2.835775000	-0.009724000
6	-0.627482000	-2.383476000	0.926376000
1	-1.232050000	-1.498808000	1.128679000
6	1.365527000	-1.333630000	2.108982000
1	-0.775757000	-3.111390000	1.731071000
6	1.980032000	-1.943864000	-1.408606000
6	1.182356000	-3.116131000	-1.987044000
1	2.433738000	-1.115450000	2.020173000
6	3.351061000	-2.385287000	-0.896658000
1	1.214124000	-1.993874000	2.969009000
1	0.827000000	-0.400497000	2.284092000
1	3.876677000	-1.533679000	-0.462954000
1	3.943207000	-2.767381000	-1.734001000
1	3.273306000	-3.189922000	-0.157236000

Scheme 168: **TS_A**

6	2.825922000	2.620883000	-1.723188000
53	-0.684496000	2.421599000	-2.592509000
1	2.434918000	3.155626000	-2.594369000
6	2.711049000	1.140964000	-1.943092000
1	3.878224000	2.866912000	-1.572683000
7	1.277979000	-1.424149000	-0.497015000
6	1.443483000	0.448196000	-2.029174000
8	3.674429000	0.390080000	-2.098092000
1	2.228001000	2.921137000	-0.855567000
8	0.438324000	0.639679000	0.059795000
6	-0.557302000	3.992779000	-1.182457000
1	1.309484000	-3.048104000	0.752622000
6	-0.505589000	5.312028000	-1.627381000
1	2.026740000	-1.636380000	-2.409970000
1	-0.546666000	5.541075000	-2.686995000
6	-0.403319000	6.335780000	-0.685476000
1	1.439397000	-4.008431000	-2.720495000
6	-0.348044000	6.037694000	0.675160000
1	-0.366045000	7.367177000	-1.021999000
1	0.015234000	-3.061659000	-2.244131000
6	-0.393858000	4.710675000	1.098120000
1	-0.266385000	6.838318000	1.403270000
1	0.825804000	-4.118284000	-1.068201000
6	-0.498888000	3.672068000	0.172034000
1	-0.345877000	4.473100000	2.156285000
1	-0.509027000	2.634229000	0.488263000
6	1.020672000	-0.120136000	-0.724749000
6	0.950056000	-2.016496000	0.814617000
1	-1.067627000	-2.571595000	0.235617000
6	-0.558878000	-2.059811000	1.057909000
1	-0.961525000	-1.049057000	1.145229000
6	1.711909000	-1.332649000	1.950831000
1	-0.766604000	-2.604920000	1.984039000
6	1.904609000	-2.272899000	-1.526062000
6	0.986899000	-3.433639000	-1.907589000
1	2.786476000	-1.332109000	1.744947000
6	3.296471000	-2.732152000	-1.098103000
1	1.538547000	-1.874850000	2.885300000
1	1.375554000	-0.301913000	2.076106000
1	3.933514000	-1.866781000	-0.901783000
1	3.752565000	-3.322351000	-1.898103000
1	3.252870000	-3.361235000	-0.202264000

Scheme 168: **B**

6	2.086747000	2.722150000	-2.227822000
53	-2.309188000	3.035734000	-2.242985000
1	1.316803000	3.161570000	-2.869458000
6	2.303840000	1.281806000	-2.611492000
1	3.026298000	3.266368000	-2.329101000
7	1.252089000	-1.354599000	-0.689621000
6	1.145477000	0.383470000	-2.586259000
8	3.375685000	0.835325000	-2.998124000
1	1.712237000	2.784005000	-1.199173000
8	0.131208000	0.677616000	-1.197538000
6	-0.961482000	3.824287000	-0.825479000
1	1.045043000	-2.525450000	0.986513000
6	-0.309242000	5.025749000	-1.095866000
1	2.587334000	-1.828212000	-2.178126000
1	-0.509676000	5.563628000	-2.016600000
6	0.614931000	5.521693000	-0.176398000
1	2.517092000	-4.289943000	-1.881668000
6	0.879348000	4.826195000	1.002047000
1	1.129420000	6.453919000	-0.387801000
1	0.881510000	-3.635482000	-2.087398000
6	0.210765000	3.631128000	1.264603000
1	1.600763000	5.214725000	1.713535000
1	1.457842000	-4.127556000	-0.478465000
6	-0.713297000	3.122585000	0.352114000
1	0.408963000	3.086475000	2.183211000
1	-1.218888000	2.182115000	0.542254000
6	0.933376000	-0.306535000	-1.407278000
6	0.608487000	-1.591273000	0.620717000
1	-1.107209000	-2.595556000	-0.248823000

6	-0.897666000	-1.787338000	0.457246000
1	-1.369096000	-0.872458000	0.087797000
6	0.955073000	-0.472978000	1.603362000
1	-1.343835000	-2.043753000	1.422206000
6	2.304508000	-2.253825000	-1.209149000
6	1.750265000	-3.659067000	-1.424443000
1	2.038713000	-0.375397000	1.715257000
6	3.528957000	-2.230452000	-0.298926000
1	0.521758000	-0.692222000	2.583506000
1	0.556527000	0.481993000	1.248728000
1	3.921847000	-1.214422000	-0.208940000
1	4.312654000	-2.864630000	-0.721801000
1	3.294026000	-2.612491000	0.700833000

Scheme 168: **B'**

6	0.675886000	3.222321000	-1.877053000
1	-0.077835000	3.759030000	-2.460042000
6	0.765534000	1.798033000	-2.362117000
1	1.649924000	3.699240000	-1.988474000
7	-0.224482000	-0.964054000	-0.589205000
6	-0.435728000	0.964548000	-2.274520000
8	1.764044000	1.325008000	-2.888329000
1	0.349241000	3.241266000	-0.832954000
8	-1.272912000	1.166748000	-0.757193000
1	-0.307495000	-2.317109000	0.953448000
1	0.902736000	-1.325788000	-2.269969000
1	0.754779000	-3.796921000	-2.219799000
1	-0.863073000	-3.074476000	-2.146745000
1	-0.114705000	-3.754709000	-0.683828000
6	-0.559178000	0.169685000	-1.150767000
6	-0.737711000	-1.332315000	0.749052000
1	-2.578391000	-2.177411000	-0.031286000
6	-2.259691000	-1.456678000	0.726807000
1	-2.721026000	-0.490288000	0.506957000
6	-0.241286000	-0.354321000	1.812881000
1	-2.616983000	-1.797335000	1.702547000
6	0.717440000	-1.840007000	-1.320663000
6	0.078962000	-3.196122000	-1.605713000
1	0.850309000	-0.287495000	1.800262000
6	2.040117000	-1.948635000	-0.568344000
1	-0.556972000	-0.695355000	2.802865000
1	-0.655985000	0.642284000	1.640997000
1	2.487969000	-0.960151000	-0.437458000
1	2.736932000	-2.568583000	-1.138696000
1	1.906379000	-2.412712000	0.415140000

Scheme 168: **TS_B**

6	1.383260000	2.976303000	-1.849573000
1	1.129612000	3.521775000	-2.762250000
6	1.463973000	1.494632000	-2.174894000
1	2.373239000	3.285387000	-1.508111000
7	-0.125148000	-0.868885000	-0.448366000
6	0.193721000	0.832189000	-2.037838000
8	2.476801000	0.944070000	-2.588193000
1	0.625309000	3.184815000	-1.089772000
8	-0.781945000	1.318991000	0.002519000
1	-0.256131000	-2.557464000	0.706950000
1	0.683448000	-0.835513000	-2.341951000
1	0.292442000	-3.194834000	-2.912950000
1	-1.207328000	-2.383929000	-2.405142000
1	-0.379602000	-3.513241000	-1.309523000
6	-0.278888000	0.445728000	-0.699893000
6	-0.558362000	-1.508084000	0.800667000
1	-2.566898000	-1.915912000	0.083667000
6	-2.078841000	-1.446456000	0.942648000
1	-2.407215000	-0.405968000	1.008014000
6	0.163336000	-0.905503000	2.006883000
1	-2.391611000	-1.970791000	1.850305000
6	0.590133000	-1.584621000	-1.502695000
6	-0.229693000	-2.737927000	-2.068724000
1	1.248015000	-0.968712000	1.879167000
6	2.002909000	-1.973581000	-1.090333000
1	-0.111595000	-1.451222000	2.914119000
1	-0.115563000	0.143699000	2.130343000
1	2.569044000	-1.092658000	-0.779728000
1	2.527531000	-2.439325000	-1.928352000
1	1.968647000	-2.692263000	-0.263194000

Scheme 168: **307**

6	1.426226000	2.534899000	-2.075354000
1	0.539206000	2.860305000	-2.629014000
6	1.637115000	1.055971000	-2.269199000
1	2.307185000	3.081161000	-2.411769000
7	-0.219753000	-0.872505000	-0.260539000
6	0.451746000	0.173601000	-1.930400000
8	2.667401000	0.587143000	-2.704018000
1	1.214268000	2.740738000	-1.021298000
8	-0.828971000	1.398282000	-0.093173000
1	-0.350042000	-2.627242000	0.781891000
1	-0.236475000	0.211742000	-2.785381000
1	0.603925000	-2.518200000	-3.164438000
1	-1.008292000	-2.099585000	-2.535101000
1	-0.014901000	-3.320189000	-1.712063000
6	-0.322636000	0.429819000	-0.621605000
6	-0.646191000	-1.581430000	0.937681000
1	-2.656573000	-1.933299000	0.197700000
6	-2.166612000	-1.504957000	1.076492000

1	-2.477586000	-0.460632000	1.174303000
6	0.069536000	-1.030906000	2.172339000
1	-2.495828000	-2.053012000	1.963918000
6	0.642070000	-1.281074000	-1.394958000
6	0.014643000	-2.368772000	-2.254745000
1	1.154465000	-1.113292000	2.062062000
6	2.044485000	-1.658946000	-0.935713000
1	-0.232655000	-1.583123000	3.067019000
1	-0.188241000	0.023706000	2.308938000
1	2.498192000	-0.855223000	-0.349409000
1	2.692255000	-1.860270000	-1.791027000
1	1.990135000	-2.558510000	-0.311335000

Scheme 169: Phenyliodonium **362**

6	0.419012000	0.936488000	-2.529781000
8	-2.714319000	-0.588934000	0.607386000
53	-2.791191000	1.002812000	-2.010989000
1	-0.095109000	0.908007000	-3.493932000
6	-0.048434000	-0.161281000	-1.583220000
1	1.489597000	0.797527000	-2.681111000
7	-1.900931000	-2.555392000	-0.197297000
6	-1.443667000	-0.431710000	-1.383027000
6	-2.635902000	-3.326764000	0.862329000
1	-4.277289000	-1.952354000	1.370207000
8	0.804123000	-0.835506000	-0.995023000
1	0.257021000	1.925299000	-2.085430000
6	-4.123453000	-2.925126000	0.910543000
1	-4.539003000	-2.904892000	-0.102965000
1	-4.669149000	-3.681801000	1.483242000
6	-2.629169000	-4.828285000	0.532574000
6	-2.513173000	2.733619000	-0.764076000
1	-1.631103000	-5.259994000	0.453852000
6	-1.968580000	-3.090424000	2.222468000
6	-0.984278000	-3.255148000	-1.098460000
1	-3.145496000	-5.345979000	1.344967000
6	-2.556812000	3.990069000	-1.358158000
6	0.335714000	-3.713728000	-0.450326000
1	-3.176132000	-5.034613000	-0.393026000
1	-1.970255000	-2.024806000	2.460258000
6	1.220228000	-4.344509000	-1.497541000
1	-2.733109000	4.108645000	-2.423349000
1	-2.517747000	-3.625218000	3.004847000
6	2.099170000	-3.560216000	-2.253295000
6	-2.356578000	5.108632000	-0.548638000
1	-0.935748000	-3.451684000	2.215979000
6	2.879200000	-4.137328000	-3.253802000
6	2.790238000	-5.504321000	-3.516571000
1	-1.497390000	-4.116688000	-1.537080000
6	-2.103305000	4.950332000	0.812957000
1	-0.749703000	-2.580566000	-1.922318000
6	1.915926000	-6.293096000	-2.770710000
1	-2.388023000	6.100297000	-0.988781000
1	0.146394000	-4.439393000	0.346092000
6	1.138234000	-5.713675000	-1.769458000
1	0.818840000	-2.840706000	-0.009527000
6	-2.053026000	3.675658000	1.375721000
1	2.159769000	-2.495133000	-2.041686000
1	-1.939749000	5.823694000	1.436179000
1	3.561760000	-3.518476000	-3.829066000
1	3.400631000	-5.952471000	-4.294749000
6	-2.262283000	2.541948000	0.588821000
1	1.842947000	-7.359128000	-2.964890000
1	-1.853853000	3.554679000	2.435746000
1	0.462485000	-6.333716000	-1.183088000
1	-2.240258000	1.537082000	1.003959000
6	-2.035169000	-1.198028000	-0.230358000

Scheme 169: **TS_C**

6	0.761362000	1.269911000	-1.157799000
8	-1.979995000	-0.365680000	0.296741000
53	-2.574278000	1.452805000	-2.412004000
1	0.553559000	1.915697000	-2.016473000
6	0.481707000	-0.161569000	-1.523637000
1	1.813572000	1.351309000	-0.880312000
7	-1.612218000	-2.544880000	-0.358361000
6	-0.864272000	-0.663215000	-1.720492000
6	-2.345841000	-3.121604000	0.813519000
1	-3.765400000	-1.485034000	1.138104000
8	1.369886000	-0.994228000	-1.707329000
1	0.113054000	1.588043000	-0.334863000
6	-3.768307000	-2.542110000	0.879169000
1	-4.269330000	-2.667846000	-0.086034000
1	-4.339116000	-3.090217000	1.635406000
6	-2.490071000	-4.639075000	0.645446000
6	-2.790200000	3.018311000	-0.999089000
1	-1.531497000	-5.159026000	0.584438000
6	-1.573979000	-2.816603000	2.103805000
6	-0.836524000	-3.387128000	-1.268824000
1	-3.015757000	-5.022106000	1.524063000
6	-2.795066000	4.341339000	-1.435667000
6	0.520219000	-3.850583000	-0.713008000
1	-3.087343000	-4.891561000	-0.235844000
1	-1.463792000	-1.738515000	2.237085000
6	1.222492000	-4.716673000	-1.729174000
1	-2.699450000	4.578306000	-2.490062000
1	-2.117582000	-3.221004000	2.963874000
6	1.985744000	-4.134618000	-2.747201000
6	-2.928949000	5.359388000	-0.491599000

1	-0.580701000	-3.275512000	2.078388000
6	2.591192000	-4.931467000	-3.717015000
6	2.439794000	-6.317599000	-3.684680000
1	-1.435060000	-4.250831000	-1.569098000
6	-3.046890000	5.052017000	0.862911000
1	-0.653974000	-2.802079000	-2.181508000
6	1.679775000	-6.905109000	-2.674854000
1	-2.938744000	6.393592000	-0.821314000
1	0.375269000	-4.413323000	0.214782000
6	1.075429000	-6.106569000	-1.705398000
1	1.122292000	-2.967836000	-0.480458000
6	-3.031240000	3.721939000	1.278067000
1	2.100644000	-3.053541000	-2.764814000
1	-3.149226000	5.848251000	1.593163000
1	3.185257000	-4.468517000	-4.499351000
1	2.914223000	-6.936470000	-4.440074000
6	-2.903518000	2.688280000	0.349139000
1	1.560445000	-7.983818000	-2.639238000
1	-3.118241000	3.478526000	2.332409000
1	0.488597000	-6.568676000	-0.913698000
1	-2.874480000	1.649665000	0.662565000
6	-1.511572000	-1.199053000	-0.487399000

Scheme 169: **C**

6	0.232361000	1.306121000	-0.214684000
8	-2.264197000	-0.389845000	0.377002000
53	-2.305271000	2.243270000	-4.099159000
1	-0.198123000	2.189683000	-0.699516000
6	-0.048964000	0.093136000	-1.060902000
1	1.311826000	1.427160000	-0.117571000
7	-1.872323000	-2.704924000	-0.122295000
6	-1.423517000	-0.393166000	-1.135657000
6	-2.488961000	-3.290613000	1.111318000
1	-3.927461000	-1.670180000	1.408229000
8	0.801810000	-0.461315000	-1.748457000
1	-0.246706000	1.212138000	0.764302000
6	-3.916607000	-2.750744000	1.256774000
1	-4.505163000	-2.987133000	0.365399000
1	-4.390771000	-3.225196000	2.120902000
6	-2.550377000	-4.812253000	0.977295000
6	-2.380820000	3.034399000	-2.144279000
1	-1.559312000	-5.263268000	0.875084000
6	-1.635637000	-2.900980000	2.324493000
6	-1.055537000	-3.469678000	-1.081082000
1	-3.004821000	-5.214363000	1.886388000
6	-1.735804000	4.240267000	-1.869907000
6	0.389684000	-3.684852000	-0.615684000
1	-3.169757000	-5.116740000	0.128539000
1	-1.585021000	-1.813435000	2.425950000
6	1.185229000	-4.356023000	-1.708615000
1	-1.225663000	4.782343000	-2.659023000
1	-2.078279000	-3.312928000	3.236555000
6	1.719275000	-3.586261000	-2.747937000
6	-1.747311000	4.735694000	-0.566132000
1	-0.618940000	-3.293016000	2.227546000
6	2.411580000	-4.199853000	-3.789817000
6	2.576349000	-5.584992000	-3.805929000
1	-1.545989000	-4.421984000	-1.291628000
6	-2.393730000	4.031614000	0.449458000
1	-1.044272000	-2.892198000	-2.011476000
6	2.045804000	-6.356797000	-2.774183000
1	-1.243671000	5.672409000	-0.348017000
1	0.410153000	-4.292288000	0.296336000
6	1.352354000	-5.742741000	-1.731730000
1	0.825184000	-2.706323000	-0.383305000
6	-3.036275000	2.829896000	0.158427000
1	1.589318000	-2.505880000	-2.726639000
1	-2.392866000	4.417377000	1.463967000
1	2.826340000	-3.593544000	-4.589299000
1	3.117828000	-6.060829000	-4.617679000
6	-3.037241000	2.324285000	-1.141475000
1	2.174009000	-7.434956000	-2.778067000
1	-3.527655000	2.264072000	0.943738000
1	0.943891000	-6.346455000	-0.923465000
1	-3.511491000	1.374250000	-1.359006000
6	-1.840065000	-1.405159000	-0.301676000

Scheme 169: **D**

6	0.967375000	4.114349000	1.039087000
8	-1.362879000	2.325989000	0.589207000
1	0.539184000	4.886652000	0.393823000
6	1.190065000	2.852114000	0.240044000
1	1.921829000	4.448926000	1.445724000
7	-0.921437000	-0.013367000	0.451437000
6	0.008584000	2.261335000	-0.386920000
6	-2.183736000	-0.455962000	1.145941000
1	-3.451819000	0.748283000	-0.140052000
8	2.301414000	2.378832000	0.042614000
1	0.246486000	3.928599000	1.840815000
6	-3.344321000	-0.297911000	0.159561000
1	-3.180074000	-0.906739000	-0.735627000
1	-4.278481000	-0.623233000	0.627289000
6	-2.040982000	-1.919752000	1.573779000
1	-1.202558000	-2.053035000	2.264201000
6	-2.415549000	0.384068000	2.408033000
6	-0.094664000	-1.021837000	-0.242992000
1	-2.956002000	-2.206932000	2.097633000
6	1.051414000	-0.460981000	-1.086541000

1	-1.918161000	-2.601051000	0.729073000
1	-2.667347000	1.418433000	2.177014000
6	1.774163000	-1.619773000	-1.732510000
1	-3.243340000	-0.057708000	2.970262000
6	1.298399000	-2.165283000	-2.928913000
1	-1.524658000	0.373305000	3.043337000
6	1.924286000	-3.264594000	-3.511485000
6	3.040652000	-3.834831000	-2.901438000
1	0.312456000	-1.706631000	0.506428000
1	-0.759691000	-1.602261000	-0.893943000
6	3.526685000	-3.296366000	-1.711296000
1	1.738366000	0.130659000	-0.472006000
6	2.895992000	-2.196558000	-1.131354000
1	0.658743000	0.209616000	-1.856729000
1	0.434737000	-1.714197000	-3.413121000
1	1.545590000	-3.671267000	-4.444203000
1	3.533695000	-4.688646000	-3.355431000
1	4.401905000	-3.728890000	-1.236195000
1	3.284555000	-1.771098000	-0.209086000
6	-0.715078000	1.260745000	0.222434000

Scheme 169: **E**

6	0.610137000	3.951052000	-0.352542000
8	-1.871181000	2.291530000	0.226123000
1	0.081671000	4.751914000	-0.877390000
6	0.420190000	2.653733000	-1.095600000
1	1.675049000	4.177595000	-0.297334000
7	-1.386576000	-0.050216000	0.061979000
6	-0.936007000	2.128405000	-1.218439000
6	-2.090526000	-0.493732000	1.309531000
1	-3.590054000	1.097920000	1.267131000
8	1.334448000	2.061029000	-1.658320000
1	0.173138000	3.877609000	0.647953000
6	-3.538717000	0.007906000	1.262006000
1	-4.039981000	-0.363113000	0.363193000
1	-4.075424000	-0.367449000	2.138230000
6	-2.099861000	-2.020846000	1.372000000
1	-1.091866000	-2.443639000	1.410729000
6	-1.357519000	0.082898000	2.526380000
6	-0.464231000	-0.899381000	-0.712002000
1	-2.620166000	-2.319285000	2.285742000
6	0.936735000	-0.988900000	-0.094533000
1	-2.636224000	-2.454250000	0.522720000
1	-1.340141000	1.175191000	2.482172000
6	1.850991000	-1.778662000	-0.998555000
1	-1.872230000	-0.217468000	3.444137000
6	2.477161000	-1.146826000	-2.078791000
1	-0.328155000	-0.284365000	2.572612000
6	3.286386000	-1.878496000	-2.945444000
6	3.477038000	-3.245619000	-2.744764000
1	-0.904299000	-1.890604000	-0.835285000
1	-0.382707000	-0.448373000	-1.706582000
6	2.854037000	-3.880781000	-1.672065000
1	0.887610000	-1.457930000	0.894856000
6	2.044364000	-3.148610000	-0.805158000
1	1.322509000	0.029107000	0.031520000
1	2.325719000	-0.079189000	-2.227536000
1	3.772928000	-1.378139000	-3.777086000
1	4.110871000	-3.813328000	-3.418967000
1	3.001724000	-4.943783000	-1.507088000
1	1.564177000	-3.644832000	0.036095000
6	-1.380220000	1.214429000	-0.286727000

Scheme 169: **TS_D**

6	0.915972000	3.972547000	0.389732000
8	-1.492632000	2.226191000	0.678365000
1	0.264982000	4.542417000	-0.276414000
6	1.247280000	2.615997000	-0.199955000
1	1.859981000	4.495263000	0.549274000
7	-1.007377000	-0.049913000	0.518684000
6	0.096320000	1.850874000	-0.662475000
6	-2.239226000	-0.473894000	1.266202000
1	-3.537666000	0.986920000	0.308218000
8	2.395101000	2.224932000	-0.352177000
1	0.377300000	3.838978000	1.331725000
6	-3.479721000	-0.094364000	0.447399000
1	-3.452262000	-0.579329000	-0.534437000
1	-4.382857000	-0.428992000	0.967264000
6	-2.221102000	-1.989983000	1.479798000
1	-1.344896000	-2.308284000	2.053453000
6	-2.257456000	0.198294000	2.645409000
6	-0.272054000	-1.012869000	-0.312184000
1	-3.111064000	-2.258316000	2.054513000
6	1.116980000	-0.515919000	-0.711483000
1	-2.255535000	-2.546577000	0.539200000
1	-2.350011000	1.280969000	2.565420000
6	1.854571000	-1.569135000	-1.501416000
1	-3.108090000	-0.185233000	3.217438000
6	1.541589000	-1.805907000	-2.843540000
1	-1.339552000	-0.040336000	3.191794000
6	2.196174000	-2.806634000	-3.557879000
6	3.173246000	-3.583530000	-2.936598000
1	-0.142511000	-1.935365000	0.253892000
1	-0.851776000	-1.256739000	-1.214845000
6	3.493567000	-3.352323000	-1.600580000
1	1.691308000	-0.232054000	0.174828000
6	2.837120000	-2.349735000	-0.888651000
1	1.035514000	0.384384000	-1.356220000

1	0.789630000	-1.191966000	-3.334627000
1	1.948563000	-2.975690000	-4.601285000
1	3.687072000	-4.360798000	-3.493359000
1	4.260097000	-3.946550000	-1.112858000
1	3.096332000	-2.162293000	0.150319000
6	-0.832113000	1.257462000	0.252953000

Scheme 169: **47**

6	1.532412000	3.141483000	-0.416937000
8	-1.206708000	2.007553000	0.573487000
1	1.611365000	3.178911000	-1.509177000
6	1.720626000	1.721924000	0.042957000
1	2.293243000	3.781296000	0.029754000
7	-1.123700000	-0.293211000	0.783328000
6	0.645542000	0.723292000	-0.386116000
6	-2.479949000	-0.475109000	1.361745000
1	-3.408947000	0.992724000	0.058003000
8	2.661864000	1.365072000	0.718024000
1	0.524822000	3.473634000	-0.147458000
6	-3.528656000	-0.060458000	0.321945000
1	-3.432224000	-0.669516000	-0.583836000
1	-4.534905000	-0.207874000	0.726466000
6	-2.676240000	-1.947248000	1.733056000
1	-1.938007000	-2.274712000	2.471786000
6	-2.609244000	0.370192000	2.634481000
6	-0.348586000	-1.386914000	0.198171000
1	-3.668852000	-2.063109000	2.176392000
6	1.007523000	-0.739166000	-0.126795000
1	-2.622643000	-2.605850000	0.860858000
1	-2.506131000	1.432915000	2.415635000
6	1.790511000	-1.400971000	-1.235368000
1	-3.591068000	0.193890000	3.085283000
6	1.216106000	-1.648624000	-2.487859000
1	-1.840205000	0.081032000	3.357598000
6	1.957328000	-2.239718000	-3.507635000
6	3.289821000	-2.589489000	-3.291594000
1	-0.231784000	-2.213577000	0.901259000
1	-0.841331000	-1.775519000	-0.704822000
6	3.874379000	-2.338479000	-2.052493000
1	1.616084000	-0.750442000	0.783339000
6	3.128518000	-1.747454000	-1.033439000
1	0.406674000	0.908063000	-1.443578000
1	0.179912000	-1.375201000	-2.675606000
1	1.494751000	-2.425782000	-4.472153000
1	3.867722000	-3.051640000	-4.085801000
1	4.913325000	-2.599768000	-1.876492000
1	3.588765000	-1.537828000	-0.071452000
6	-0.666318000	0.927678000	0.386939000

Scheme 169: **TS_E**

6	0.441264000	3.976658000	-0.834494000
8	-1.900204000	2.329362000	0.706172000
1	0.418466000	4.538523000	-1.771482000
6	0.627348000	2.501920000	-1.167659000
1	1.316488000	4.279152000	-0.255134000
7	-1.301638000	0.110396000	0.282174000
6	-0.625318000	1.815436000	-1.164286000
6	-2.045629000	-0.557627000	1.380872000
1	-3.611971000	0.955333000	1.538377000
8	1.708502000	2.019404000	-1.484402000
1	-0.476673000	4.167733000	-0.273749000
6	-3.513817000	-0.112503000	1.340859000
1	-3.949973000	-0.331089000	0.361194000
1	-4.075129000	-0.664943000	2.100665000
6	-1.993681000	-2.073011000	1.173406000
1	-0.972515000	-2.465042000	1.181743000
6	-1.409213000	-0.177570000	2.723056000
6	-0.350011000	-0.541046000	-0.600013000
1	-2.537186000	-2.551038000	1.992571000
6	1.038434000	-0.817684000	-0.009982000
1	-2.476951000	-2.363792000	0.235500000
1	-1.427104000	0.907466000	2.853672000
6	1.854463000	-1.680590000	-0.943173000
1	-1.967075000	-0.637089000	3.545135000
6	2.579778000	-1.110094000	-1.994174000
1	-0.371924000	-0.522683000	2.775710000
6	3.288763000	-1.921653000	-2.878569000
6	3.281671000	-3.307230000	-2.725249000
1	-0.777152000	-1.444340000	-1.047779000
1	-0.233114000	0.158731000	-1.489585000
6	2.560696000	-3.882268000	-1.680138000
1	0.912644000	-1.330595000	0.949762000
6	1.851517000	-3.071073000	-0.796731000
1	1.543832000	0.133744000	0.184582000
1	2.584684000	-0.029125000	-2.106877000
1	3.852294000	-1.467355000	-3.687927000
1	3.839441000	-3.935532000	-3.412783000
1	2.554789000	-4.960009000	-1.548775000
1	1.297413000	-3.523349000	0.023692000
6	-1.335408000	1.446975000	0.068720000

Scheme 169: **46**

6	0.610660000	2.965993000	-2.013887000
8	-2.185911000	2.231233000	0.057608000
1	0.682712000	2.588171000	-3.039013000
6	0.718822000	1.825312000	-1.034901000
1	1.398028000	3.695309000	-1.825728000

7	-1.375247000	0.067179000	0.600382000
6	-0.422006000	0.829788000	-1.107694000
6	-2.082680000	-0.521598000	1.744636000
1	-3.164989000	1.305260000	2.236607000
8	1.592243000	1.765981000	-0.195455000
1	-0.375189000	3.432162000	-1.900468000
6	-3.374329000	0.263185000	1.988113000
1	-4.012937000	0.251559000	1.100385000
1	-3.916163000	-0.200622000	2.817868000
6	-2.416373000	-1.976627000	1.401075000
1	-1.512103000	-2.564629000	1.211757000
6	-1.184923000	-0.451623000	2.986306000
6	-0.397162000	-0.519490000	-0.337730000
1	-2.945857000	-2.439907000	2.238539000
6	0.903697000	-1.068801000	0.247437000
1	-3.057602000	-2.027564000	0.515402000
1	-0.924628000	0.588242000	3.203048000
6	1.823414000	-1.543012000	-0.855829000
1	-1.708237000	-0.869632000	3.852485000
6	2.981712000	-0.835923000	-1.191128000
1	-0.259376000	-1.015633000	2.839761000
6	3.807719000	-1.276649000	-2.224789000
6	3.486880000	-2.428655000	-2.939563000
1	-0.867394000	-1.303441000	-0.948083000
1	-0.818105000	0.762083000	-2.123677000
6	2.336426000	-3.144754000	-2.610162000
1	0.649360000	-1.920772000	0.890321000
6	1.515198000	-2.703835000	-1.575367000
1	1.388744000	-0.309457000	0.861948000
1	3.230117000	0.064935000	-0.638801000
1	4.705834000	-0.717706000	-2.469558000
1	4.131179000	-2.770953000	-3.743387000
1	2.082927000	-4.049515000	-3.154248000
1	0.627757000	-3.277192000	-1.312644000
6	-1.507420000	1.239103000	-0.078662000

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